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Neuro-Ophthalmology

2019–2020
BCSC
Basic and Clinical
Science Course™

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Neuro-Ophthalmology

Last major revision 2017-2018

2019-2020
BCSC
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Cover image: From BCSC Section 9, *Uveitis and Ocular Inflammation*. Large mutton-fat keratic precipitates in a patient with sarcoidosis. (Courtesy of Debra Goldstein, MD.)



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General Introduction

The Basic and Clinical Science Course (BCSC) is designed to meet the needs of residents and practitioners for a comprehensive yet concise curriculum of the field of ophthalmology. The BCSC has developed from its original brief outline format, which relied heavily on outside readings, to a more convenient and educationally useful self-contained text. The Academy updates and revises the course annually, with the goals of integrating the basic science and clinical practice of ophthalmology and of keeping ophthalmologists current with new developments in the various subspecialties.

The BCSC incorporates the effort and expertise of more than 90 ophthalmologists, organized into 13 Section faculties, working with Academy editorial staff. In addition, the course continues to benefit from many lasting contributions made by the faculties of previous editions. Members of the Academy Practicing Ophthalmologists Advisory Committee for Education, Committee on Aging, and Vision Rehabilitation Committee review every volume before major revisions. Members of the European Board of Ophthalmology, organized into Section faculties, also review each volume before major revisions, focusing primarily on differences between American and European ophthalmology practice.

Organization of the Course

The Basic and Clinical Science Course comprises 13 volumes, incorporating fundamental ophthalmic knowledge, subspecialty areas, and special topics:

- 1 Update on General Medicine
- 2 Fundamentals and Principles of Ophthalmology
- 3 Clinical Optics
- 4 Ophthalmic Pathology and Intraocular Tumors
- 5 Neuro-Ophthalmology
- 6 Pediatric Ophthalmology and Strabismus
- 7 Oculofacial Plastic and Orbital Surgery
- 8 External Disease and Cornea
- 9 Uveitis and Ocular Inflammation
- 10 Glaucoma
- 11 Lens and Cataract
- 12 Retina and Vitreous
- 13 Refractive Surgery

In addition, a comprehensive Master Index allows the reader to easily locate subjects throughout the entire series.

References

Readers who wish to explore specific topics in greater detail may consult the references cited within each chapter and listed in the Basic Texts section at the back of the book.

These references are intended to be selective rather than exhaustive, chosen by the BCSC faculty as being important, current, and readily available to residents and practitioners.

Multimedia

This edition of Section 5, *Neuro-Ophthalmology*, includes videos related to topics covered in the book. The videos were selected by members of the BCSC faculty and are available to readers of the print and electronic versions of Section 5 (www.aao.org/bcscvideo_section05). Mobile-device users can scan the QR code below (a QR-code reader must already be installed on the device) to access the video content.



Self-Assessment and CME Credit

Each volume of the BCSC is designed as an independent study activity for ophthalmology residents and practitioners. The learning objectives for this volume are given on page 1. The text, illustrations, and references provide the information necessary to achieve the objectives; the study questions allow readers to test their understanding of the material and their mastery of the objectives. Physicians who wish to claim CME credit for this educational activity may do so by following the instructions given at the end of the book.

This Section of the BCSC has been approved by the American Board of Ophthalmology as a Maintenance of Certification (MOC) Part II self-assessment CME activity.

Conclusion

The Basic and Clinical Science Course has expanded greatly over the years, with the addition of much new text, numerous illustrations, and video content. Recent editions have sought to place greater emphasis on clinical applicability while maintaining a solid foundation in basic science. As with any educational program, it reflects the experience of its authors. As its faculties change and medicine progresses, new viewpoints emerge on controversial subjects and techniques. Not all alternate approaches can be included in this series; as with any educational endeavor, the learner should seek additional sources, including Academy Preferred Practice Pattern Guidelines.

The BCSC faculty and staff continually strive to improve the educational usefulness of the course; you, the reader, can contribute to this ongoing process. If you have any suggestions or questions about the series, please do not hesitate to contact the faculty or the editors.

The authors, editors, and reviewers hope that your study of the BCSC will be of lasting value and that each Section will serve as a practical resource for quality patient care.

Objectives

Upon completion of BCSC Section 5, *Neuro-Ophthalmology*, the reader should be able to

- describe a symptom-driven approach to the assessment of patients with common neuro-ophthalmic clinical manifestations in order to formulate an appropriate differential diagnosis
 - select the most appropriate tests and imaging studies necessary, based on clinical signs and symptoms, to diagnose and manage neuro-ophthalmic disorders in a cost-effective manner
 - identify the anatomical structures relevant to neuro-ophthalmic disorders (including the skull base, orbit, brain, vascular system, and cranial nerves) in order to localize lesions
 - describe eye movement disorders and their relation to the ocular motor system
 - describe the association between the pupil, eyelid position, and ocular motor pathology in order to identify disease processes
 - explain the pathophysiology and management of diplopia and central eye movement disorders
 - identify the effects of systemic disorders on the afferent and efferent pathways of the visual system
 - explain the possible neurologic and systemic effects of neuro-ophthalmic disorders
-

Introduction

The Basic and Clinical Science Course has undergone continuous evolution since its inception. These volumes originated as a topic outline with suggested reading lists, including primary and secondary sources for each topic. In recent years, the books have grown into far more detailed reviews of each of the ophthalmic subspecialties, taking on many of the attributes of textbooks.

Section 5, *Neuro-Ophthalmology*, has likewise evolved. In 2001, the text was reorganized to take a symptom-driven approach, focusing on how to approach patients with neuro-ophthalmic complaints. The emphasis is on the examination of the patient—both basic and extended—and the appropriate use of adjunctive studies to determine the status of the patient’s visual system as a whole. With this edition, we hope the reader will find the content to be improved in terms of both the approach to the diagnosis and to the management of a patient with neuro-ophthalmic disease. We have also continued to revise and update the content, illustrative material (figures), tables, and references. One particularly significant modification for this edition is Chapter 8’s title change from “The Patient With Diplopia” to “The Patient With Abnormal Ocular Motility or Diplopia.” This title change reflects that not all patients with abnormal ocular motility will have diplopia, and that not all patients with diplopia will have abnormal eye movements. In addition, Chapters 7 and 8 switched position from the previous edition; “The Patient With Supranuclear Disorders of Ocular Motility” now follows “The Patient With Abnormal Ocular Motility or Diplopia.” These chapters were swapped so that the reader will now read an introduction on the basic concepts of eye movements and examination findings prior to delving into the potentially daunting task of understanding supranuclear ocular motility disorders and nystagmus (Chapter 9).

This book is in no way meant to be an all-encompassing or comprehensive treatise; thus, we have included a list of some of the more useful secondary sources of information, as well as references with primary source material. As with all the prior major revisions, we have endeavored to make this book more readable as well as clinically relevant and hope that it will help to instill confidence in ophthalmologists to approach patients with common clinical neuro-ophthalmic problems.

In several chapters throughout the book, you will see links to the NOVEL (Neuro-Ophthalmology Virtual Education Library) website of NANOS (North American Neuro-Ophthalmology Society). This is a web-accessible collection of images, video, lectures, and other digital media, containing open-access, copyrighted resources. Once you have accessed the collections, you can navigate through to the relevant resources. See the NOVEL website for more information: <http://novel.utah.edu>.

Neuro-Ophthalmic Anatomy

Medical practice in general—and surgical subspecialties in particular—is an exercise in applied anatomy. Although an adequate understanding of physiology and, increasingly, molecular genetics is important in understanding disease and potential treatments, anatomy is the foundation. The anatomy of the globe and adnexal structures is covered in more detail in BCSC Section 2, *Fundamentals and Principles of Ophthalmology*; Section 7, *Oculofacial Plastic and Orbital Surgery*; and Section 8, *External Disease and Cornea*. This chapter outlines the intracranial pathways subserving the afferent and efferent visual pathways. It also briefly discusses the sensory and motor anatomy of the face and the autonomic nervous system as applied to the eye and visual system.

Bony Anatomy

Skull Base

The skull base has an intimate relationship with visually essential structures (Fig 1-1). The skull base is connected to the lower facial skeleton by 3 sets of pillars formed by the *maxillary* and *zygomatic bones* anteriorly and the *pterygoid process* of the sphenoid bone posteriorly. Superiorly, the vault of the skull is made up of the *parietal bones*, which meet at the *sagittal suture*; the *frontal bone*, which adjoins them at the *coronal suture*; and the occipital bone, which meets the parietal bones at the *lambdoid suture*.

The *sella turcica*, located posteriorly and medially to the 2 orbits, is a skull-based depression within the body of the *sphenoid bone*. The lesser wing of the sphenoid bone is pierced by the *optic canal*, which allows the optic nerves to exit from the orbit. The *superior orbital fissure*, which transmits the ocular motor cranial nerves (CNs) (oculomotor nerve or CN III, trochlear nerve or CN IV, and abducens nerve or CN VI), the ophthalmic division of the sensory trigeminal nerve (CN V₁), the sympathetic fibers, and the superior ophthalmic vein (Fig 1-2), represents the gap between the lesser and greater wings of the sphenoid bone. The parasellar region is connected laterally to the *petrous* and *temporal bones* and inferiorly to the *clivus*, extending to the *foramen magnum* and the exit of the spinal cord. The posterior skull base is enclosed by the *occipital bones*.

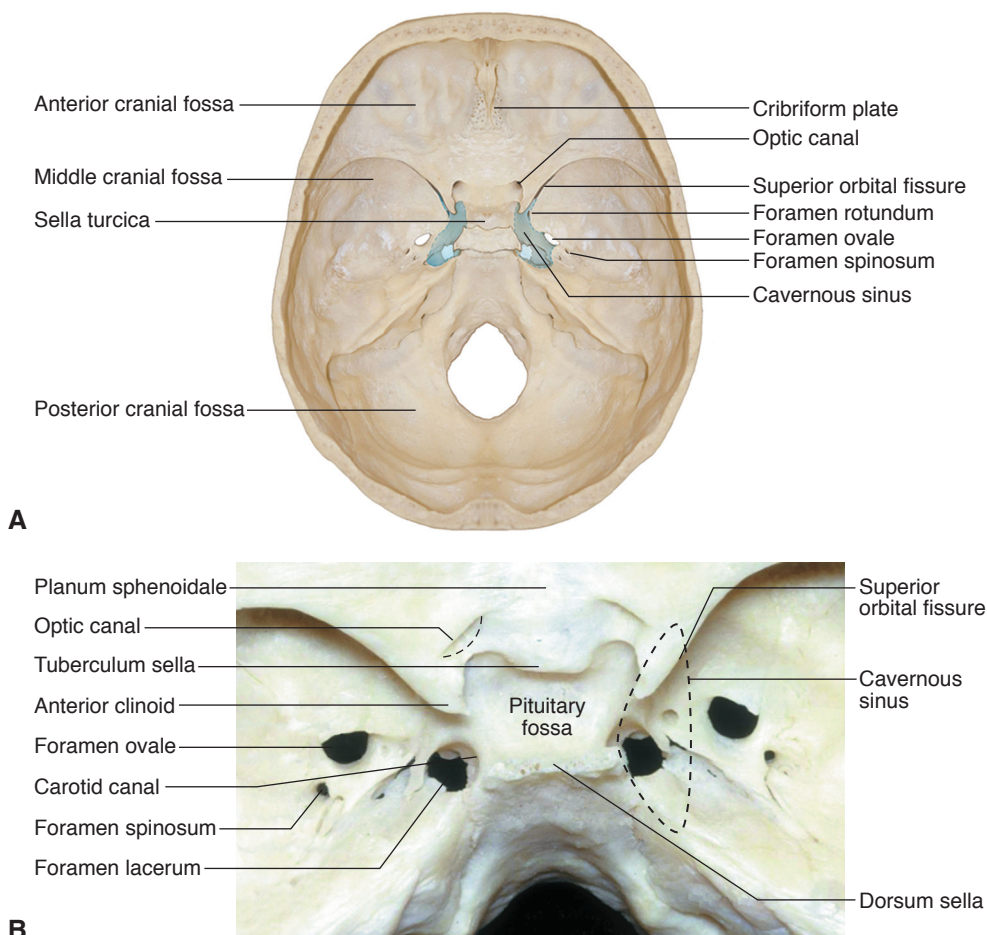


Figure 1-1 Bony anatomy of the skull base. **A**, General view of the skull base. The cavernous sinuses are located on each side of the sella turcica. Important openings within the skull base include the cribriform plate (transmits branches of the olfactory nerve, also known as cranial nerve [CN] I), optic canal (transmits the optic nerve, CN II), foramen ovale (transmits the mandibular division [CN V₃] of the trigeminal nerve, CN V), foramen rotundum (transmits the maxillary division [CN V₂] of CN V), superior orbital fissure (transmits CNs III, IV, VI, and V [ophthalmic division, CN V₁]), and the foramen spinosum (transmits the middle meningeal artery, a branch of the external carotid artery). **B**, View of the parasellar bony anatomy demonstrates the relationship of the pituitary fossa to the cavernous sinus, including the foramina of the skull base. The foramen lacerum is filled with cartilage and contains the artery of the pterygoid canal, the nerve of the pterygoid canal, and venous drainage structures. The carotid artery enters the skull base through the carotid canal. (Courtesy of Albert L. Rhoton Jr, MD.)

The Orbit

The orbit—connected posteriorly to the parasellar region—makes up the anterior aspect of the skull and is composed of 7 craniofacial bones (Fig 1-3):

1. maxillary
2. zygomatic
3. frontal

4. lacrimal
5. sphenoid
6. palatine
7. ethmoidal

The orbit is approximately 45 mm wide and 35 mm in maximal height. The total volume of the orbit is approximately 30 cm³. The medial wall is approximately 40 mm from the rim to the optic canal. The medial walls are roughly parallel, whereas the lateral walls form an angle of almost 90°. The orbital rim is made up of the *frontal bone* superiorly, which connects to the *zygomatic bone* (at the *frontozygomatic suture*) laterally. The inferior orbital rim is made up of the zygomatic bone inferolaterally and the maxillary

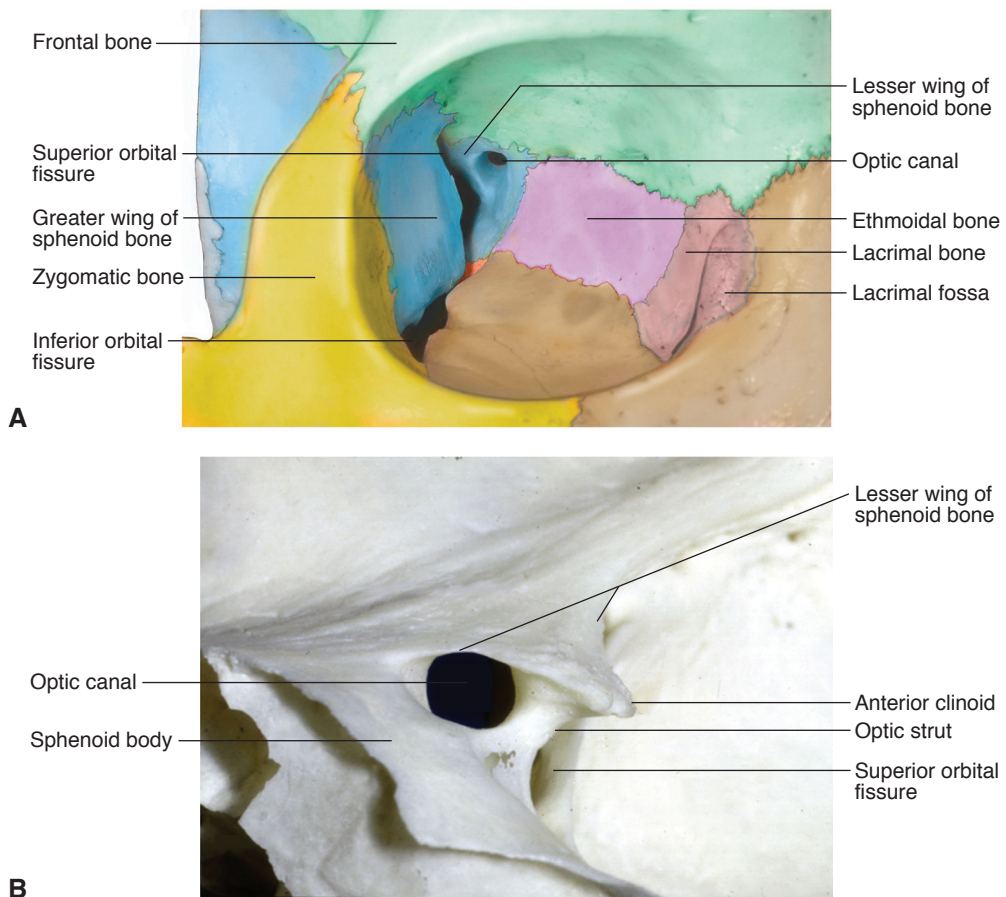


Figure 1-2 Anatomy of the orbit. **A**, Bony anatomy of the right orbital apex. The optic canal transmits the optic nerve, ophthalmic artery, and oculosympathetic nerves. The superior orbital fissure, a gap between the greater and lesser wings of the sphenoid bones, transmits CNs III, IV, and VI; the ophthalmic division (CN V₁) of CN V; and the superior ophthalmic vein. **B**, Intracranial view of the left optic canal. Within the lesser wing of the sphenoid bone is the optic foramen, which leads to the optic canal. The optic strut separates the optic canal from the superior orbital fissure.

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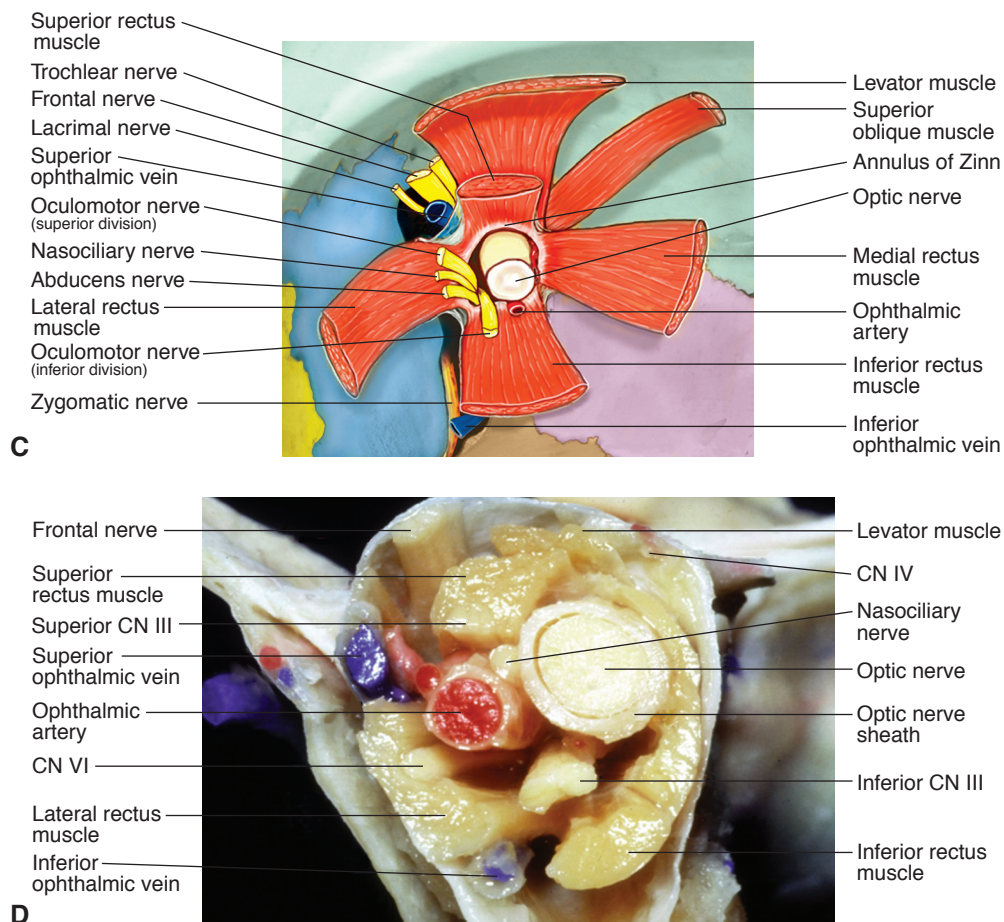


Figure 1-2 (continued) **C**, Anatomy of the orbital apex. The 4 rectus muscles arise from the annulus of Zinn. CNs II, III (superior and inferior branches), and VI and the nasociliary nerve all course through the annulus of Zinn. CN IV, the frontal and lacrimal nerves, and the ophthalmic veins are located outside the annulus. **D**, Anatomical dissection just anterior to the superior orbital fissure. (Parts A and C illustrations by Dave Peace; parts B and D courtesy of Albert L. Rhoton Jr, MD.)

bone inferonasally (meeting at the *zygomaticomaxillary suture*). Medially, the orbital rim consists of the *maxillary* and *lacrimal* bones, which join the frontal bone superiorly. An additional 3 bones contribute to the orbit: (1) the *ethmoidal bone* medially, (2) the *palatine bone* inferiorly in the posterior orbit, and (3) the *sphenoid bone* laterally and superiorly in the orbital apex.

The orbit is surrounded by several important structures. The 4 *paranasal sinuses* surround the floor (*maxillary sinus*) and the medial wall (*ethmoidal* and *sphenoid sinuses*) of the orbit (Fig 1-4). The *frontal sinus* has a variable relationship to the anterior orbital roof. The other major structures around the orbit are the *anterior cranial fossa* superiorly (containing the frontal lobe) and the *temporal fossa* laterally (containing the temporalis muscle). The roof of the *ethmoidal complex*, delineated by the *frontal ethmoidal suture* (top of the *ethmoidal bone*, or *lamina papyracea*), marks the inferior boundary of the anterior cranial fossa. It is important to realize that surgical intervention above this anatomical

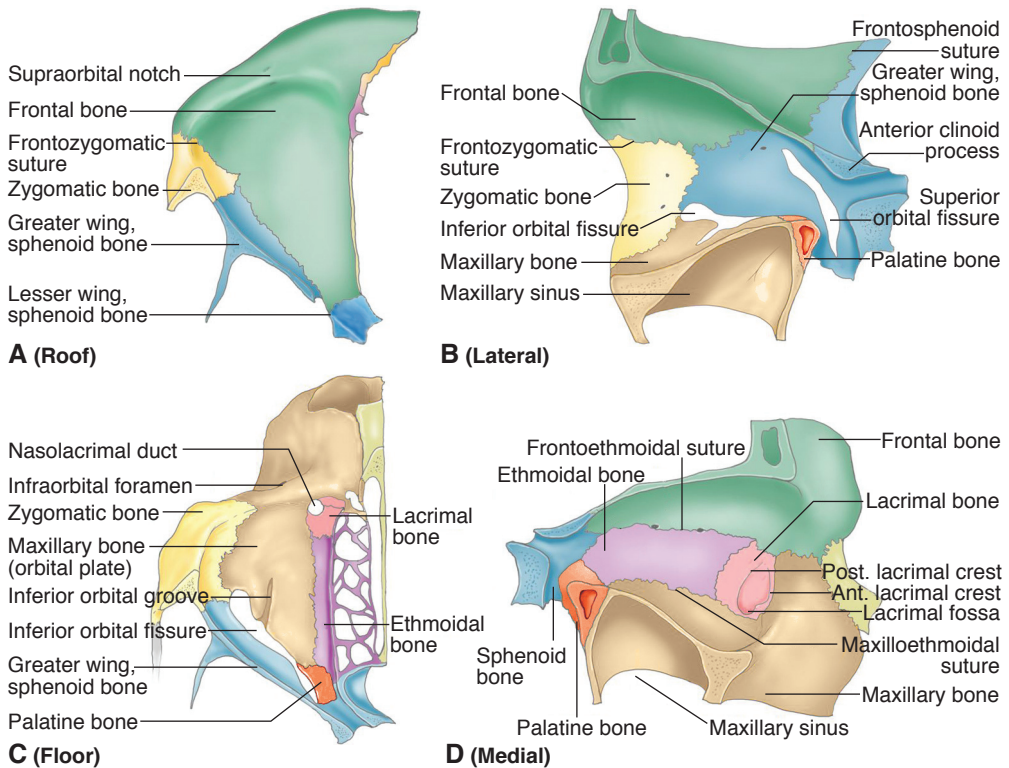


Figure 1-3 Bony anatomy of the right orbit. **A**, The orbital roof is composed of 2 bones: (1) the frontal bone and (2) the lesser wing of the sphenoid bone. The frontal sinus lies within the anterior orbital roof. The supraorbital notch, located within the medial one-third of the superior orbital rim, transmits the supraorbital nerve, a terminal branch of the frontal nerve of the ophthalmic division of CN V. Medially, the frontal bone forms the roof of the ethmoidal sinus and extends to the cribriform plate. **B**, The lateral orbital wall is formed by the zygomatic bone and the greater wing of the sphenoid bone. The junction between the lateral orbital wall and the roof is represented by the frontosphenoid and frontozygomatic sutures. Posteriorly, the wall is bordered by the inferior and superior orbital fissures. The sphenoid wing makes up the posterior portion of the lateral wall and separates the orbit from the middle cranial fossa. Medially, the lateral orbital wall ends at the inferior and superior orbital fissures. **C**, The orbital floor is composed of 3 bones: (1) the orbital plate of the maxillary bone, (2) the maxillary process of the zygomatic bone, and (3) the palatine bone. The nasolacrimal duct sits in the anterior medial area of the orbital floor, medial to the origin of the inferior oblique muscle. **D**, The medial orbital wall is formed by 4 bones: (1) maxillary (frontal process), (2) lacrimal, (3) sphenoid, and (4) ethmoidal. The largest component of the medial wall is the lamina papyracea of the ethmoidal bone. Superiorly, the anterior and posterior foramina at the level of the frontoethmoidal suture transmit the anterior and posterior ethmoidal arteries, respectively. The anterior medial orbital wall includes the lacrimal sac fossa, formed by the maxillary and lacrimal bones. The lacrimal bone is divided by the posterior lacrimal crest. The anterior part of the lacrimal sac fossa is formed by the anterior lacrimal crest of the maxillary bone. (Illustrations by Dave Peace.)

landmark—as occurs, for example, during endoscopic sinus surgery—can result in entry into the anterior cranial fossa or a cerebrospinal fluid (CSF) leak.

The sphenoid sinus forms the medial wall of the optic canal (Fig 1-5). Surgery within the sphenoid sinus has the potential to damage the optic nerve; alternatively, the sphenoid sinus is a surgical route facilitating decompression of the optic chiasm. In approximately

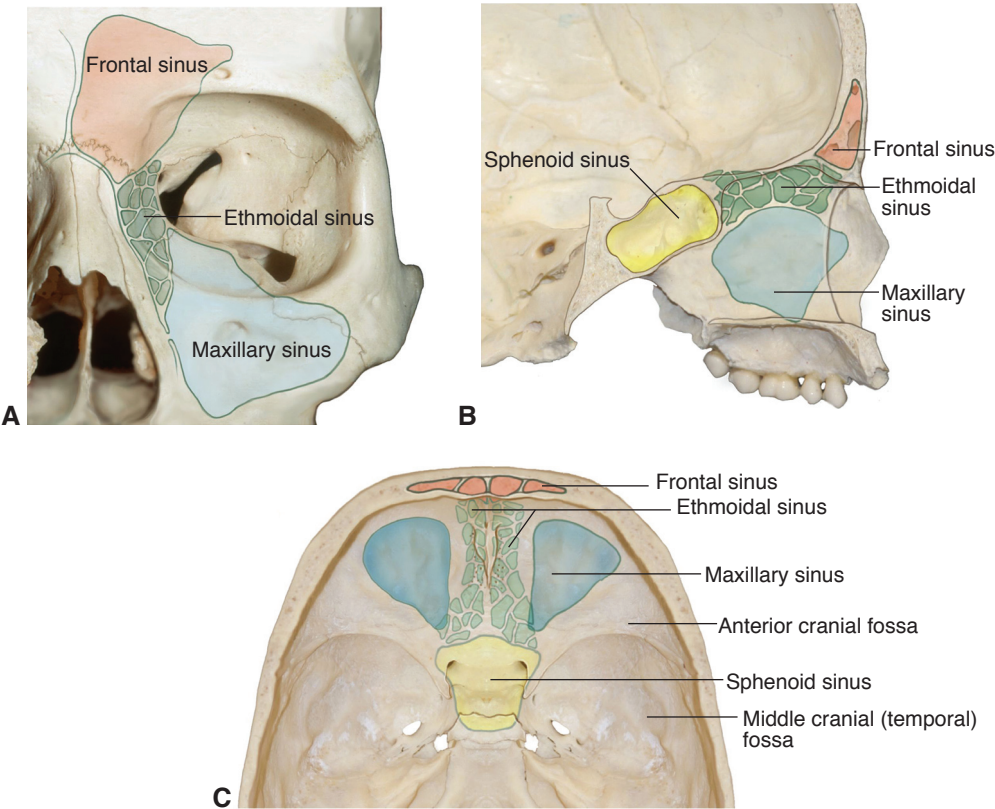


Figure 1-4 Coronal (A), sagittal (B), and axial (C) views of the anatomical relationship of the 4 paranasal sinuses to the orbit. (Illustrations by Dave Peace.)

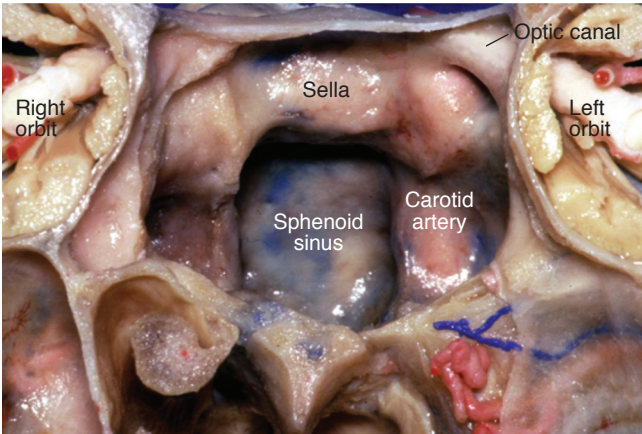


Figure 1-5 Coronal section, anterior view into the sphenoid sinus demonstrating the relationship of the internal carotid artery and optic nerve within the lateral wall of the sinus. (Courtesy of Albert L. Rhoton Jr, MD.)

4% of patients, the bone may be incomplete, leaving only mucosa separating the sinus from the optic nerve. The *pterygomaxillary area*, which contains the sphenopalatine ganglion and the internal maxillary artery, underlies the apex of the orbit. This area communicates posteriorly through the *foramen rotundum* and the *vidian canal* to the *middle cranial fossa*, anteriorly through the *infraorbital canal* to the cheek and lower eyelid, and superiorly through the *inferior orbital fissure* to the orbit.

Canals and fissures

The orbit communicates with the surrounding areas through several bony canals and fissures. Posteriorly, the orbit is contiguous with the *cavernous sinus* through the superior orbital fissure (see Fig 1-2). The medial wall of the orbit continues as the lateral wall of the sphenoid bone, marking the medial extent of the cavernous sinus. Therefore, when sharp objects enter the medial orbit, they are directed through the superior orbital fissure, where they can lacerate the carotid artery.

The orbit is connected superiorly and posteriorly to the anterior cranial fossa by way of the *optic canal* (see Fig 1-2B), which transmits the optic nerve, ophthalmic artery, and some sympathetic fibers. Inferiorly at the apex, the orbit is connected to the *pterygopalatine area*—and thus the temporal and inferotemporal regions—through the inferior orbital fissure. This fissure, formed by the greater wing of the sphenoid, maxillary, zygomatic, and palatine bones, carries the maxillary branch of CN V (CN V₂), infraorbital vessels, the inferior ophthalmic vein, branches from the pterygopalatine ganglion, parasympathetic fibers that innervate the lacrimal gland, and collateral meningeal arteries that help connect the external and internal carotid circulation.

Anteriorly, the orbit connects to the *inferior meatus* of the nose (beneath the inferior turbinate) through the *nasolacrimal duct*, which carries tears into the nasal cavity. In addition, numerous variable bony canals carry blood vessels that travel to and from the orbit and surrounding structures. Some of the more constant of these canals include the *anterior* and *posterior ethmoidal foramina*, which carry blood vessels connecting the internal carotid circulation (ophthalmic artery) to the external carotid circulation (terminal branches of the ethmoidal arteries) at the level of the roof of the ethmoidal complex. Additional supraorbital and *zygomaticotemporal foramina* carry blood vessels between the orbit and corresponding vessels of the forehead and temple.

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Vascular Anatomy

Arterial System

Knowledge of the vascular anatomy of the head is crucial to understanding the potential for ischemic damage to the visual system. Ischemia is among the most common pathophysiologic causes of visual dysfunction (including vision loss and double vision). The

common carotid arteries, arising from the *innominate artery* on the right and directly from the aorta on the left, supply most of the blood to the skull and its contents. The remainder of the blood supply to the skull comes from the 2 *vertebral arteries* (VAs), which enter the skull through the foramen magnum after traversing foramina in the cervical vertebral segments. Once the VAs penetrate the dura, they join near the pontomedullary junction to form the *basilar artery* (BA), which ascends along the anterior surface of the pons to terminate in the 2 *posterior cerebral arteries* (PCAs) at the level of the midbrain.

The common carotid artery divides into internal and external branches at the angle of the jaw (Fig 1-6). The *external carotid artery* (ECA) supplies blood to the face through its major branches of the *facial artery* (FA). The scalp is supplied via branches of the *occipital artery* posteriorly and the *superficial temporal artery* anteriorly. The paranasal sinuses receive their blood supply from branches of the *maxillary artery* (sphenopalatine and infraorbital), which terminates in the pterygopalatine fossa. The coverings of the brain are supplied by branches of the *middle meningeal artery* (MMA)—a major branch of the maxillary artery—which enters the middle cranial fossa through the foramen spinosum, lateral to the foramen ovale. Branches of the MMA supply the parasellar area, including the lateral wall of the cavernous sinus (containing CNs III, IV, and VI), and terminate in the arteries of the foramen rotundum and ovale. Variable meningeal branches may enter the superior orbital fissure.

Ophthalmologists are sometimes concerned about encountering branches of CN VII, particularly when performing a temporal artery biopsy or during orbital or lacrimal surgery. Terminal branches of the FA supply the marginal arcades of the eyelids. It is extremely important to understand the extent of the collateral connections between the branches of the ECA and the *internal carotid artery* (ICA) (Fig 1-7). This point is particularly germane to interventional neuroradiologists, who may inadvertently embolize distal ICA branches—including the *central retinal artery* (CRA)—while placing particles into the ECA. Embolization is most likely to occur during the treatment of arteriovenous malformations, but it can also occur when skull-base tumors are embolized prior to surgical resection.

The most important collateral connections between the internal and external circulations traverse the orbit. They include the *anterior* and *posterior ethmoidal arteries* in the medial orbit, the *infraorbital* and *supraorbital arteries* (including distal connections to the lacrimal artery) anteriorly, and the zygomaticotemporal branch laterally. The FA joins the distal branches of the *supratrochlear* and *infratrochlear arteries* around the *angular artery* in the medial orbit. In addition, variable collateral dural branches traverse the superior and inferior orbital fissures. In rare instances, the *ophthalmic artery* (OphA) may also arise as a branch of the meningeal system of the ECA.

The ICA carries the major blood supply to the intracranial contents (Fig 1-8). The ICA enters the skull through the carotid canal. Within the petrous bone, the ICA is near the middle and inner ear, as well as the intrapetrous portion of CN VII. As the ICA reaches the parasellar area, it turns superiorly just above the foramen lacerum. It then enters the cavernous sinus, where it first gives off the *meningohypophyseal trunk* and then turns anteriorly to run horizontally parallel to the body of the sphenoid to give off the inferolateral trunk, which forms anastomoses with branches of the MMA. Branches of the meningohypophyseal trunk supply the dura at the back of the cavernous sinus as

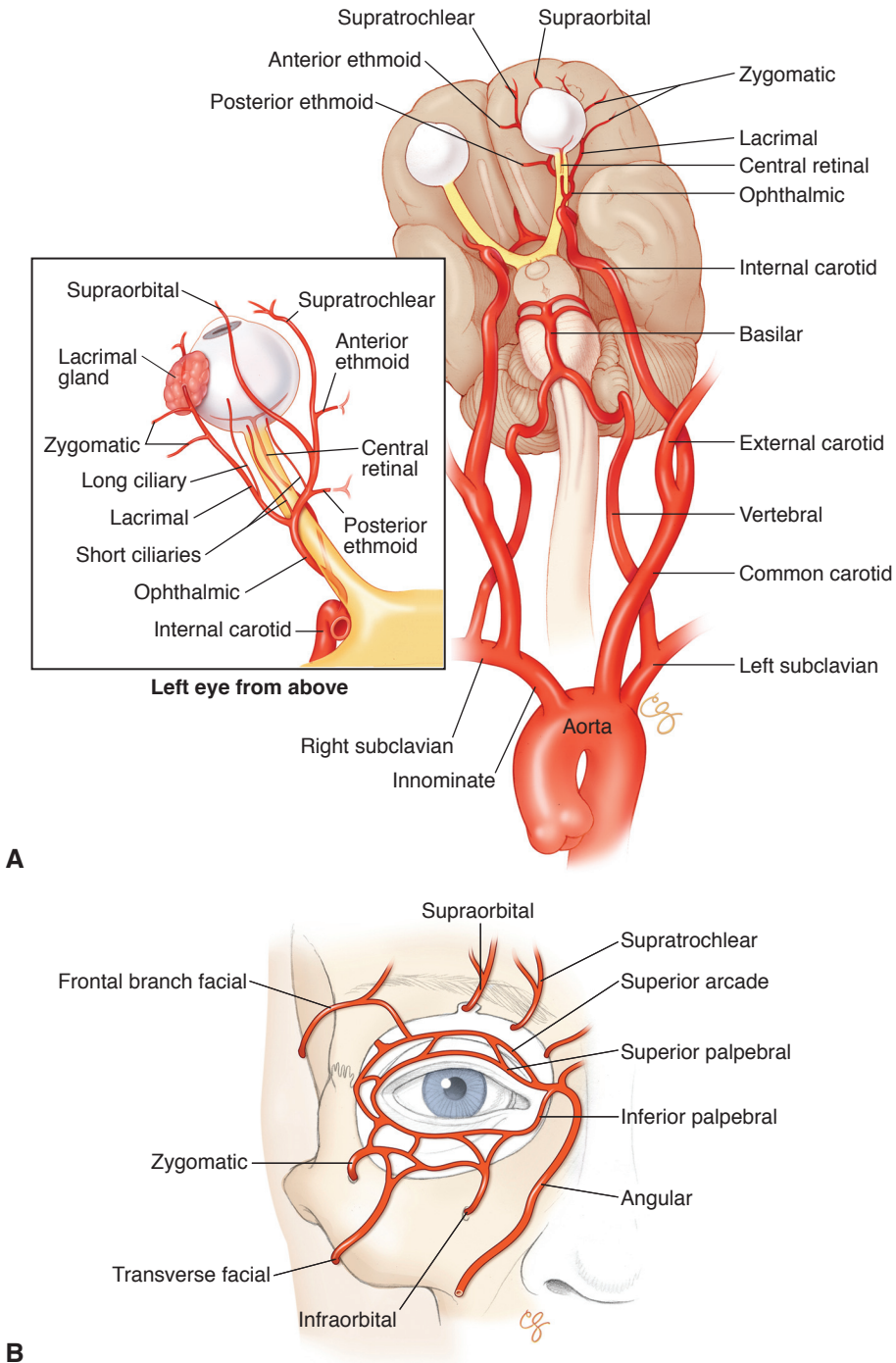


Figure 1-6 Arterial supply of the orbit and ocular adnexa. **A**, Arterial supply of the ocular adnexa and orbit originating from the aortic arch. **B**, Anterior view of the superficial arterial supply to the eyelids and anterior orbit.

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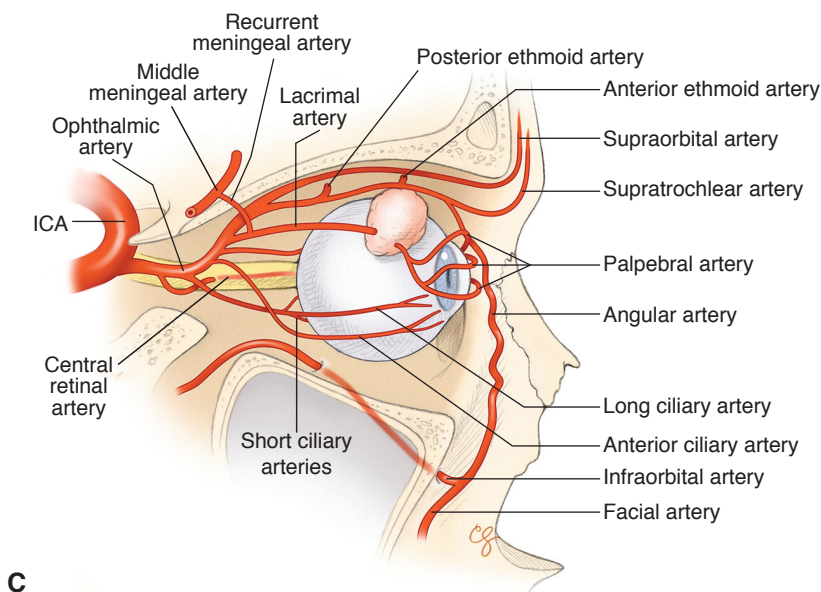


Figure 1-6 (continued) C, Sagittal view of the arterial supply to the orbit and globe. ICA = internal carotid artery. (Illustrations by Christine Gralapp.)

well as CNs III, IV, V, and VI entering the cavernous sinus. These branches also variably supply the lateral aspect of the sella turcica, including the pituitary capsule and a large portion of the pituitary gland itself.

At the anterior aspect of the cavernous sinus, the ICA makes a loop to reverse its direction under the anterior clinoid and the optic nerve. This loop passes through 2 dural rings, both close to the anterior clinoid (the terminal portion of the lesser wing of the sphenoid). As the ICA passes through the second ring, it becomes intradural (Fig 1-9). Just after it becomes intradural, the ICA gives off the OphA, which enters the orbit along with the optic nerve through the optic canal.

Within the orbit, the OphA (see Fig 1-7) may anastomose with recurrent meningeal branches that enter through the superior orbital fissure. The OphA gives off the CRA, which then enters the substance of the optic nerve approximately 10–12 mm posterior to the globe. Within the eye, the CRA divides into superior and inferior arcades. Like the blood–brain barrier, the retinal arteries and arterioles have tight junctions that form a blood–retina barrier. The intraretinal arterioles run within the substance of the nerve fiber layer to supply the inner two-thirds of the retina.

The *lacrimal artery* (LA) runs parallel to the lacrimal branch of CN V₁ in the superior lateral orbital roof to reach the lacrimal gland. It also gives off the *anterior ciliary artery* of the lateral rectus muscle and reaches the anterior segment at the muscle's insertion. The *frontal artery* runs within the superior orbit, paralleling the frontal branch of CN V₁ to separate into and terminate as the supraorbital and supratrochlear arteries, which, along with the LA, supply the eyelid.

The next branches leaving the OphA are the *superior* and *inferior muscular arteries*, which supply the anterior ciliary arteries of the medial and inferior rectus (inferior

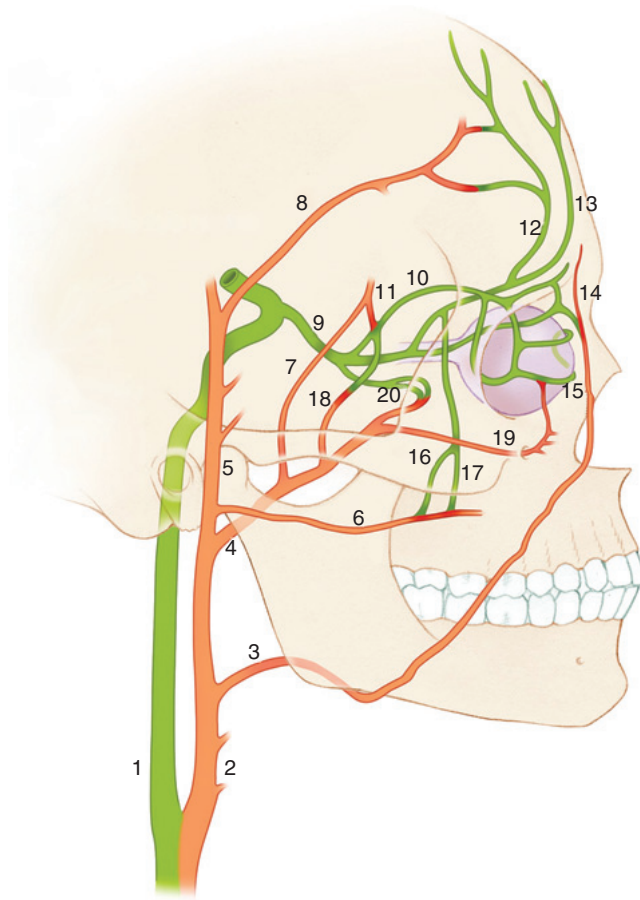


Figure 1-7 Internal carotid artery (green) and external carotid artery (orange) collateral anatomy. 1, internal carotid; 2, external carotid; 3, facial; 4, maxillary; 5, superficial temporal; 6, transverse facial; 7, middle meningeal; 8, frontal branch of superficial temporal; 9, ophthalmic; 10, lacrimal; 11, recurrent meningeal; 12, supraorbital; 13, supratrochlear; 14, angular; 15, palpebral; 16, zygomaticotemporal; 17, zygomaticofacial; 18, deep temporal; 19, infraorbital; 20, muscular. (Modified with permission from Kline LB. *Neuro-Ophthalmology Review Manual*. 6th ed. Thorofare, NJ: Slack; 2008:213, by Christine Gralapp.)

muscular artery) and the superior rectus and superior oblique (superior muscular branch) muscles. The anterior ciliary arteries are responsible for the majority of blood flow to the ciliary body. The *medial* and *lateral long posterior ciliary arteries* variably anastomose with penetrating branches of the anterior ciliary arteries (within the rectus muscles) to form the *greater arterial circle* near the anterior part of the ciliary body. Branches from this circle extend radially within the iris to form a second anastomotic circle (the *lesser arterial circle*) near the collarette of the iris.

The terminal OphA supplies additional branches that form collaterals with the *anterior* and *posterior ethmoidal arteries* and also form the *short* and *long posterior ciliary arteries* (Fig 1-10). The short posterior ciliary arteries divide into 10–20 small branches that supply the optic nerve head (ONH) and posterior choroid. Together, these arteries

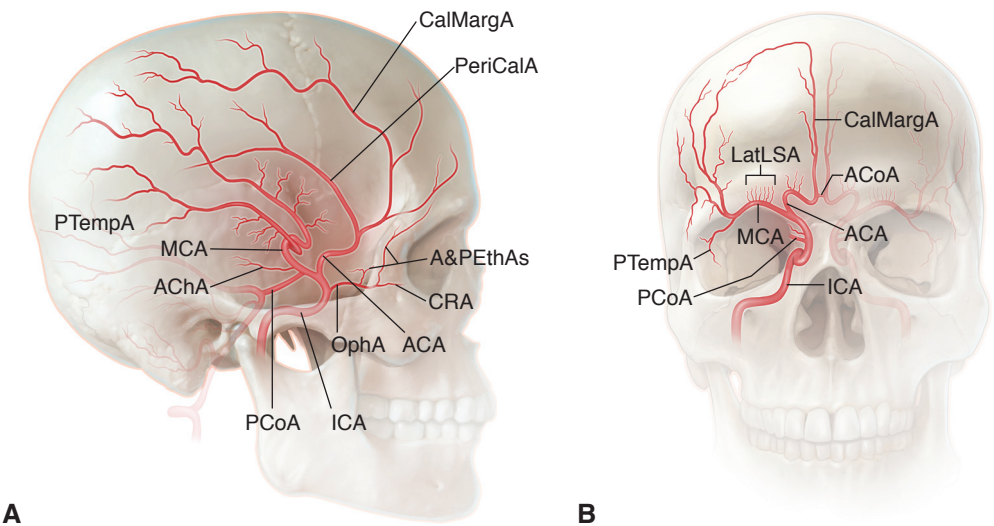


Figure 1-8 Branches of the ICA. **A**, Lateral view. **B**, Anteroposterior view. Proximal ICA branches: ophthalmic artery (OphA) and its branches (anterior and posterior ethmoidal arteries [A&PEthAs] and central retinal artery [CRA]); posterior communicating artery (PCoA); anterior choroidal artery (AChA); anterior communicating artery (ACoA); anterior cerebral artery (ACA) and its branches (callosomarginal artery [CalMarga] and pericallosal artery [PeriCalA]); and middle cerebral artery (MCA) and its branches (lateral lenticulostriate artery [LatLSA] and posterior temporal artery [PTempA]). (Illustrations by Rob Flewell, CMI.)

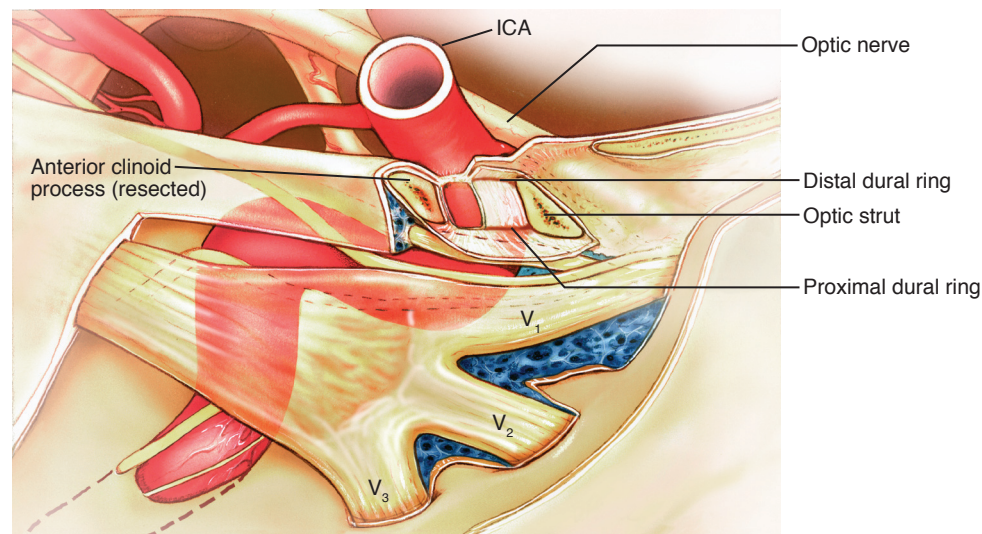


Figure 1-9 Lateral view of the bend of ICA within the right cavernous sinus. The anterior clinoid process has been resected to show the proximal and distal dural rings. V₁ = ophthalmic division of CN V; V₂ = maxillary division of CN V; V₃ = mandibular division of CN V. (Illustration by Dave Peace.)

supply blood to the choroid, the retinal pigment epithelium (RPE), and approximately the outer one-third of the retina, including the photoreceptor cells. In approximately 30% of individuals, branches of the posterior ciliary arteries (*cilioretinal arteries*) directly supply a portion of the inner retina; this blood supply may protect the macula in the case of a CRA occlusion. Approximately 4 short posterior ciliary arteries form a variably complete anastomotic ring (known as the *circle of Zinn-Haller*) around the ONH, which is also supplied from the peripapillary choroid and the terminal branches of the pial network.

Collateral branches from terminal branches of the infraorbital artery and the superficial temporal artery help supply the lower and upper eyelids and may also provide collateral supply to the anterior segment. These collaterals may be interrupted if the conjunctiva and Tenon capsule are removed from the limbus during ocular surgery.

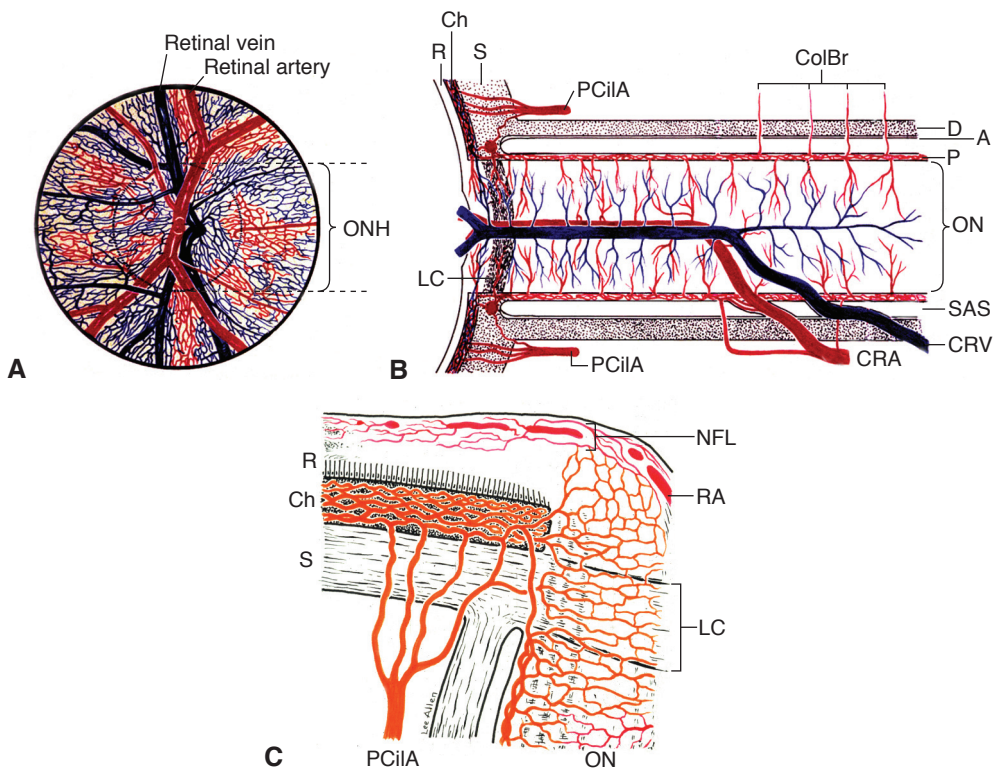


Figure 1-10 Schematic representation of the vascular supply to the optic nerve and optic nerve head (ONH). Intraocular view (A), lateral view (B), and sagittal view (C) of the ONH. Short posterior ciliary arteries supply centripetal capillary beds of the anterior ONH. The central retinal artery (CRA) contribution is restricted to nerve fiber layer capillaries and capillaries of the anterior intraorbital optic nerve. Capillary beds at all levels drain into the central retinal vein (CRV). A = arachnoid; Ch = choroid; ColBr = collateral branches; D = dura; LC = lamina cribrosa; NFL = surface nerve fiber layer of the ONH; ON = optic nerve; P = pia; PCiA = posterior ciliary artery; R = retina; RA = retinal arteriole; S = sclera; SAS = subarachnoid space. (Reproduced from Hayreh SS. The blood supply of the optic nerve head and the evaluation of it—myth and reality. *Prog Retin Eye Res.* 2001;20(5):563–593.)

Distal to the origin of the OphA, the intradural supraclinoid ICA gives off the *anterior choroidal artery (AChoA)* and anastomoses with the proximal *posterior cerebral artery (PCA)* through the *posterior communicating artery (PCoA)*. The AChoA supplies blood proximally to the optic tract and distally to the *lateral geniculate nucleus (LGN)* (Fig 1-11). Injury to the AChoA can produce the optic tract syndrome, a disorder consisting of contralateral homonymous hemianopia, contralateral band atrophy of the ONH, and a contralateral relative afferent pupillary defect (see Chapter 4). The ICA gives off the *anterior cerebral artery (ACA)* and terminates as branches of the *middle cerebral artery (MCA)*. The proximal ACA (the A1 segment) crosses over the optic nerve and joins the opposite ACA via the *anterior communicating artery (ACoA)*. The combination of the ACoA and PCoA makes up the *circle of Willis*, which permits collateral flow between the carotid and vertebrobasilar systems when there is vascular compromise. Small perforating branches arising from the proximal ACA as well as the ACoA supply the intracranial optic nerves and chiasm. Although the afferent visual pathways are spared with distal ACA occlusion, the premotor areas of the frontal lobes responsible for initiating saccades are supplied by

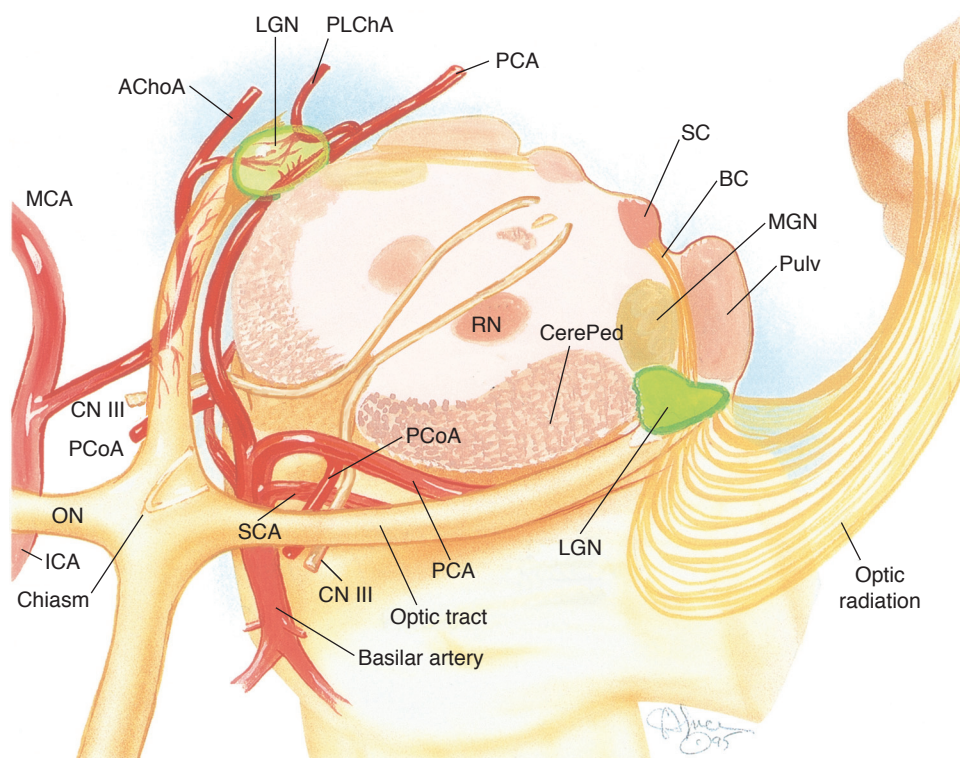


Figure 1-11 Relationship of the lateral geniculate nucleus to nearby structures and its blood supply. AChoA = anterior choroidal artery; BC = brachium conjunctivum; CerePed = cerebral peduncles; ICA = internal carotid artery; LGN = lateral geniculate nucleus; MCA = middle cerebral artery; MGN = medial geniculate nucleus; ON = optic nerve; PCA = posterior cerebral artery; PCoA = posterior communicating artery; PLChA = posterior lateral choroidal artery; Pulv = pulvinar; RN = red nucleus; SC = superior colliculus; SCA = superior cerebellar artery. (Illustration by Craig A. Luce.)

branches of the ACA. Thus, patients with acute occlusion of the ACA may have a transient gaze preference and difficulty initiating saccades to the contralateral side, although this effect is more commonly seen in patients with MCA territory lesions.

The MCA divides into several branches, which supply the temporal lobe, parietal lobe, and superficial portions of the frontal lobe and occipital lobe. Branches important to the visual pathways include those supplying the optic radiations as they traverse the deep white matter of the parietal and temporal lobes. Terminal branches of the MCA also variably supply the occipital tip representing the macula. This supply is chiefly responsible for the perimetric finding of macular sparing in PCA or calcarine artery occlusion (see Chapter 4, Fig 4-32). In addition to supplying the afferent pathways, the MCA supplies the middle temporal region, which is involved in visually guided pursuit movements. Thus, lack of blood supply can cause problems with ipsilateral pursuit or asymmetry in optokinetic nystagmus when a clinician rotates the OKN drum toward the side of the infarct.

The posterior circulation begins with the aortic arch. The right and left VAs arise from the subclavian arteries. The innominate artery becomes the right subclavian artery beyond the origin of the common carotid artery (see Fig 1-6A). The VA travels through a series of foramina in the lateral aspects of the cervical vertebral processes. After penetrating the dura at the foramen magnum, the VA gives rise to the *posterior inferior cerebellar artery (PICA)* before joining the other VA to form the BA (Fig 1-12). The PICA represents the most caudal of the 2 major circumferential arteries that wrap around the brainstem. Proximally, the PICA and BA first give off branches that perforate the medial portion of the brainstem at the medullary level; the paramedian branches that follow supply the lateral aspects of the

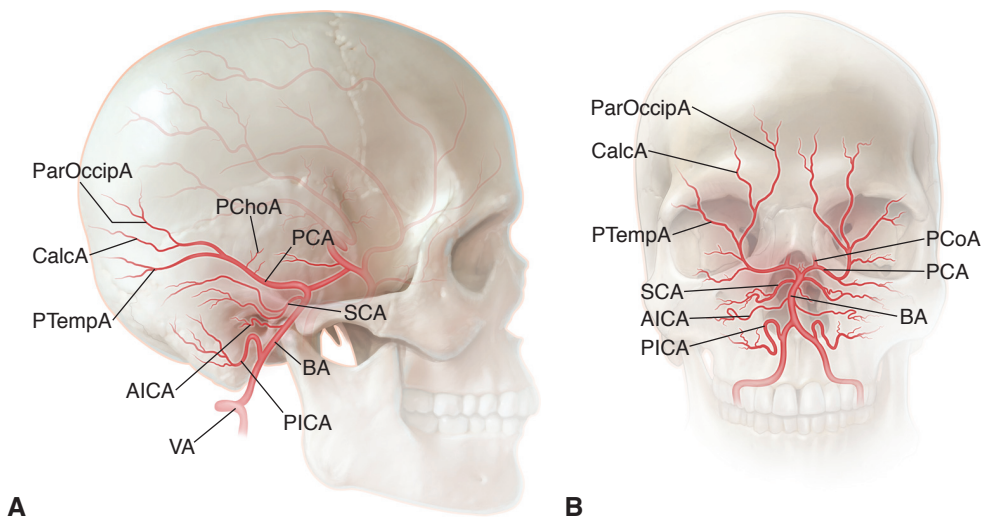


Figure 1-12 Vertebrobasilar arterial system and major arteries with common variations of the cortical branches of the posterior cerebral artery (PCA). **A**, Lateral view. **B**, Anteroposterior view. Vertebral artery (VA) and basilar artery (BA) branches: anterior inferior cerebellar artery (AICA); posterior inferior cerebellar artery (PICA); superior cerebellar artery (SCA). PCA and its branches: calcarine artery (CalcA); parieto-occipital artery (ParOccipA); posterior choroidal artery (PChoA); posterior temporal artery (PTempA); posterior communicating artery (PCoA).

(Illustration by Rob Flewell, CMI.)

brainstem. Distally, the PICA supplies the inferior cerebellum, which is intimately involved in eye movements. VA or PICA occlusion is associated with the lateral medullary syndrome (also called Wallenberg syndrome) (see Chapter 2, Fig 2-6). The second circumferential arteries are branches of the *anterior inferior cerebellar artery* (AICA). The AICA arises from the caudal BA and supplies the pontomedullary junction and distal cerebellum. A large proximal branch of the AICA, the *internal auditory artery*, supplies the CN VIII complex in the subarachnoid space and follows it into the internal auditory canal. Along the course of the BA, small perforators arise directly to supply portions of the pons and midbrain. The median perforators of the BA supply the medial longitudinal fasciculus, the paramedian pontine reticular formation (PPRF), and the medially located nuclei of CNs III, IV, and VI. Interruption of these branches (which occurs commonly with vertebrobasilar atherosclerotic disease or emboli to these end arteries) often produces variable ophthalmoplegia, internuclear ophthalmoplegia, and skew deviation. Pontine branches of the BA also supply the proximal portions of the CNs (particularly CN V) as they exit the brainstem.

The distal 2 sets of circumferential arteries consist of the *superior cerebellar artery* (SCA) followed by the PCA, representing the terminal branches of the BA at the level of the midbrain. Perforators from the proximal SCA partially supply the nucleus of CN III and its fascicles. In addition, small branches often supply the CN V root. CN III exits between the SCA and the PCA, where it may be compressed by an aneurysm.

Perforators from the proximal PCA (the P1 segment) supply the rostral portion of the midbrain (the portion involved in vertical gaze) and part of the LGN. A large branch, the *artery of Percheron*, often supplies both sides of the midbrain from one of the PCAs. Because *thalamostriate arteries* originate from P1, infarcts related to the internal ICA-MCA spare the thalamus. The P1 segment ends with the PCoA, which joins the vertebrobasilar circulation to the carotid circulation anteriorly. The connecting PCoA parallels the course of CN III and then joins the ICA, which explains the occurrence of CN III palsy with PCoA aneurysms (see Chapters 2 and 7). As the distal PCA courses around the brainstem, it gives off a *parieto-occipital branch* before terminating in the *calcarine branch*, which supplies the primary visual cortex (Fig 1-13).

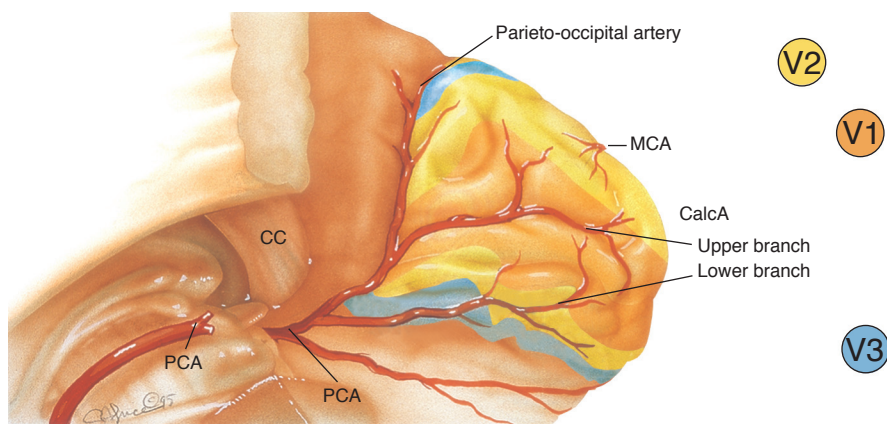


Figure 1-13 The occipital cortex and its blood supply. The primary visual cortex, or striate cortex (V1); the parastriate cortex (V2); and V3 are keyed by color. CalcA = calcarine artery; CC = corpus callosum; MCA = middle cerebral artery; PCA = posterior cerebral artery. (Illustration by Craig A. Luce.)

Venous System

Ocular venous outflow begins in the *arcade retinal veins*, which exit into the *central retinal vein (CRV)*, and in the *choroidal veins*, which exit the sclera through the *vortex veins*. Anteriorly, the episcleral venous plexus collects both blood from the anterior uveal circulation and aqueous percolating through the Schlemm canal. These 3 primary venous drainage pathways (Fig 1-14) empty mainly into the *superior ophthalmic vein*, which runs posteriorly within the superior medial orbit to the orbital apex, where it crosses laterally to enter the cavernous sinus posterior to the superior orbital fissure.

Microscopic collaterals variably exist between these venous beds. In rare instances, shunts connecting retinal veins to choroidal veins are present within the retina. More commonly (usually in association with central retinal vein occlusion or optic nerve sheath

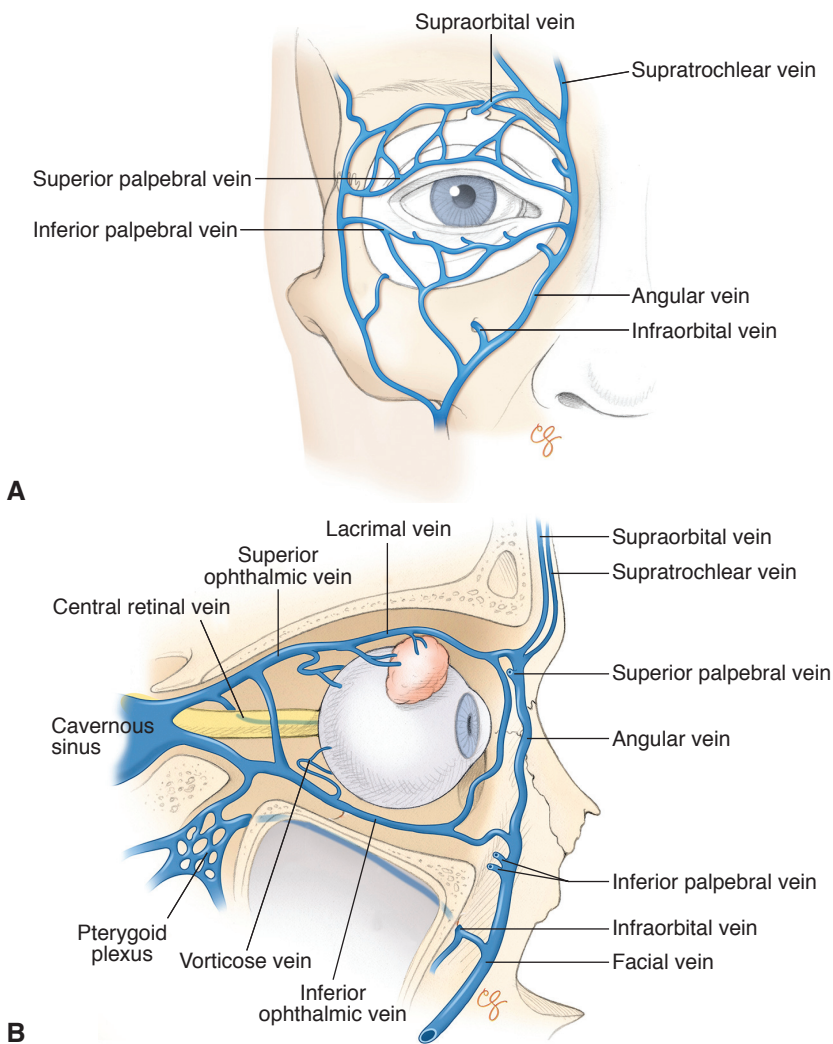


Figure 1-14 Venous drainage of the orbit. **A**, Anterior view of the superficial venous system of the eyelids. **B**, Sagittal view of the venous circulation of the orbit and globe. (Illustrations by Christine Galapp.)

meningioma), optociliary shunt vessels (retinochoroidal collateral vessels) may appear on the ONH surface. At a more macroscopic level, the superior ophthalmic vein is variably connected anteriorly to the *angular* and *facial veins* and inferiorly to the *inferior ophthalmic vein* and *pterygoid plexus*. These collaterals may become important, particularly in patients with elevated venous pressure (usually related to a carotid cavernous fistula).

Intracranially, the superficial cortical venous system drains mainly superiorly and medially to the *superior sagittal sinus* running in the sagittal midline (Fig 1-15). In addition to the cortical drainage, the superior sagittal sinus absorbs CSF through the arachnoid villi and the pacchionian granulations. Thus, obstruction to venous outflow results in decreased CSF absorption and elevated intracranial pressure. The superior sagittal sinus runs posteriorly to terminate at the *torcular Herophili* (confluence of the venous sinuses) at the level of the tentorium that separates the cerebellum from the occipital lobes. The *transverse sinuses* run anteriorly from the connection of the tentorium and the skull to the petrous pyramid, where they turn to run caudally as the *sigmoid sinus* down to the *jugular bulb*, where the *internal jugular vein* exits the skull.

Inferior superficial cortical venous drainage is carried directly down to the transverse and sigmoid sinuses through the *vein of Labbé* and the *basilar vein of Rosenthal*. The deep drainage of the supratentorial diencephalon and mesencephalon begins with the deep-draining veins (often in relationship to the ventricular system). These deep veins drain together to form the *vein of Galen*, which runs posteriorly to drain into the straight sinus. The vein of Galen runs within the tentorium to drain, along with the superior sagittal sinus, into the torcular Herophili.

Some anterior cerebral venous drainage may access the cavernous sinus. The 2 cavernous sinuses are joined by variable connections through the sella and posteriorly through a plexus of veins over the clivus. The cavernous sinus drains primarily caudally into the jugular bulb via the *inferior petrosal sinus*, which traverses the Dorello canal with CN VI under the petroclinoid ligament. Alternatively, drainage may occur laterally along the petrous apex through the *superior petrosal sinus* to the junction of the transverse and sigmoid sinuses (Fig 1-16). Small veins may drain through the foramen rotundum and foramen

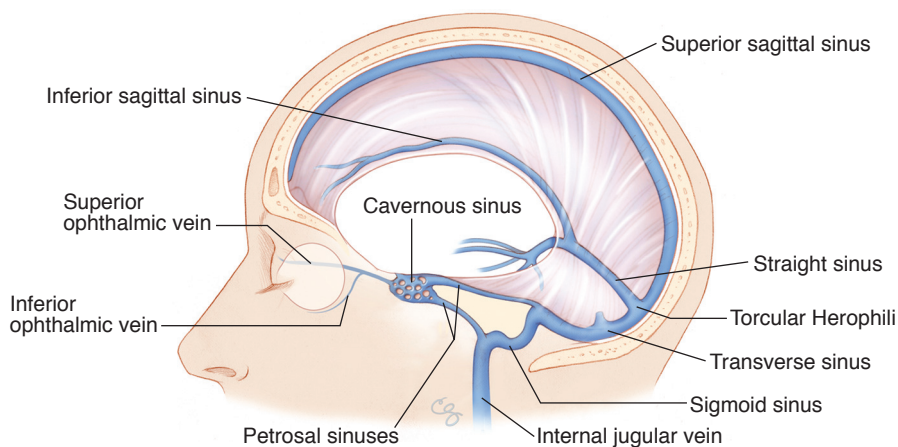


Figure 1-15 Anatomy of the cerebral venous sinus system. (Illustration by Christine Galapp.)

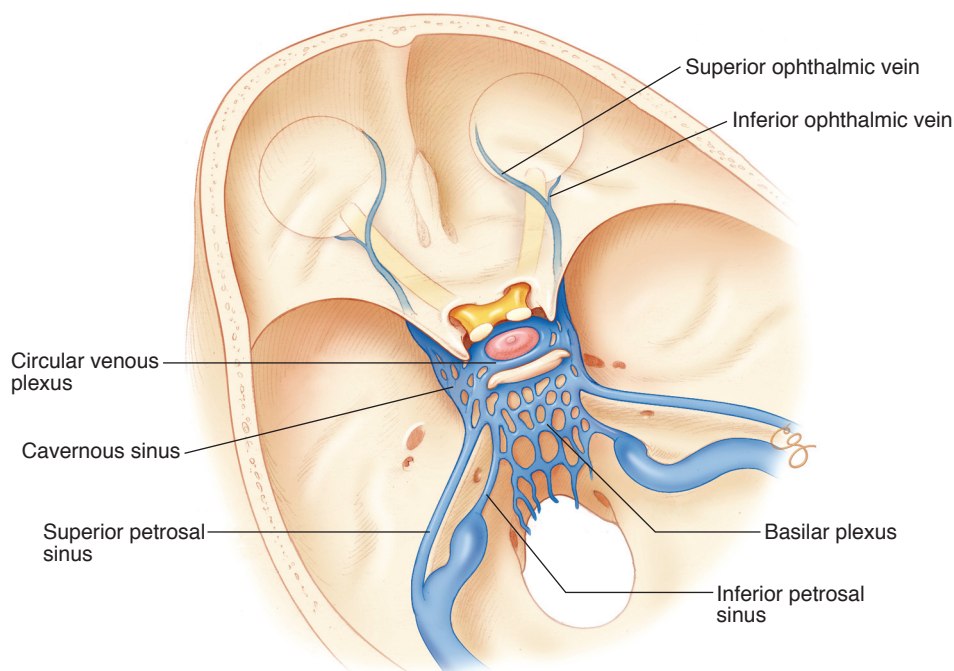


Figure 1-16 Anatomy of the cavernous sinus drainage system. (Illustration by Christine Gralapp.)

ovale as well as through the pterygoid plexus to anastomose with the *facial venous system* (*external jugular vein*).

Veins of the eyelids anastomose medially between the *angular vein* and branches of the superior ophthalmic vein (particularly at the superior medial orbit in the region of the trochlea). Facial veins drain inferiorly and laterally to form the external jugular vein, which eventually joins the internal jugular in the neck.

Hayreh SS. *Ocular Vascular Occlusive Disorders*. Switzerland: Springer International Publishing; 2015.

Kupersmith MJ. *Neuro-vascular Neuro-ophthalmology*. New York: Springer-Verlag; 1993.

Lasjaunias P, Berenstein A, ter Brugge KG. *Surgical Neuroangiography*. 2nd ed. New York: Springer; 2001. *Clinical Vascular Anatomy and Variations*; vol 1.

Vanderah T, Gould D. *Nolte's The Human Brain: An Introduction to Its Functional Anatomy*. 7th ed. St Louis: Mosby; 2016.

Afferent Visual Pathways

Any disturbance in afferent function may result in the same symptoms of vision loss as observed with pathology affecting the retina, optic nerve, and visual pathways (Fig 1-17).

Retina

The afferent visual pathway begins within the retina. Details of retinal anatomy can be found in BCSC Section 2, *Fundamentals and Principles of Ophthalmology*, and

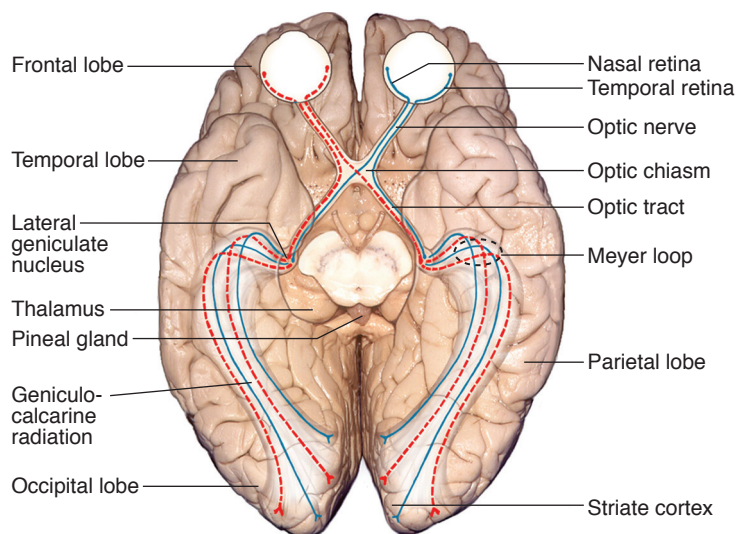


Figure 1-17 Basal view of the brain showing the anterior and posterior visual pathways. (Illustration by Dave Peace.)

Section 12, *Retina and Vitreous*. The following discussion focuses on key points relevant to neuro-ophthalmology.

The absence of retinal receptors over the ONH creates a *physiologic scotoma* (*blind spot*), located approximately 17° from the fovea and measuring approximately 5° by 7° . The fovea (approximately 1.5 mm, or 1 disc diameter) is located approximately 4 mm (or 2.5 disc diameters) from and 0.8 mm lower than the ONH.

The RPE is in direct contact with the retinal photoreceptor cells. Between the outer and inner retinal layers, the retinal signal generated in rods and cones is processed primarily through the bipolar cells that synapse on retinal ganglion cells (RGCs). A subset of melanopsin-containing RGCs, known as intrinsically photosensitive retinal ganglion cells (ipRGCs), serve primarily nonvisual light-dependent functions such as the pupillary light reflex.

Horizontal, amacrine, and interplexiform cells (which communicate horizontally between neighboring cells) permit signal processing within the retinal layers. The glial support cells—*Müller cells* and *astrocytes*—play an important metabolic role.

The ratio of photoreceptor cells to RGCs varies depending on the region of the retina. The ratio is highest in the periphery (at more than 1000:1) and lowest at the fovea (where an RGC may receive a signal from 1 single cone). Because of the increased central density of RGCs (69% within the central 30°), the foveal bipolar cells and RGCs are displaced radially from the fovea, with the bipolar cells receiving input via long cone axons that make up the *Henle layer*. The radial nature of the Henle layer is responsible for the accumulation of fluid in the macula in a star-shaped pattern.

Another notable anatomical feature of the retina is the location of the ONH and the beginning of the optic nerve nasal to the fovea. Thus, although ganglion cell fibers coming

from the nasal retina can travel uninterrupted directly to the ONH, those coming from the temporal retina must avoid the macula by anatomically separating to enter the ONH at either the superior or the inferior pole (Fig 1-18). This unique anatomy means that some of the nasal fibers (nasal within the macula) enter the ONH on its temporal side (*papillomacular bundle*). Focal loss of the nerve fiber layer may appear as either grooves or slits or as reflections that parallel the retinal arterioles where the internal limiting membrane drapes over the vessels. Diffuse loss of the nerve fiber layer is often more difficult to detect and brings the retinal vessels into sharp relief.

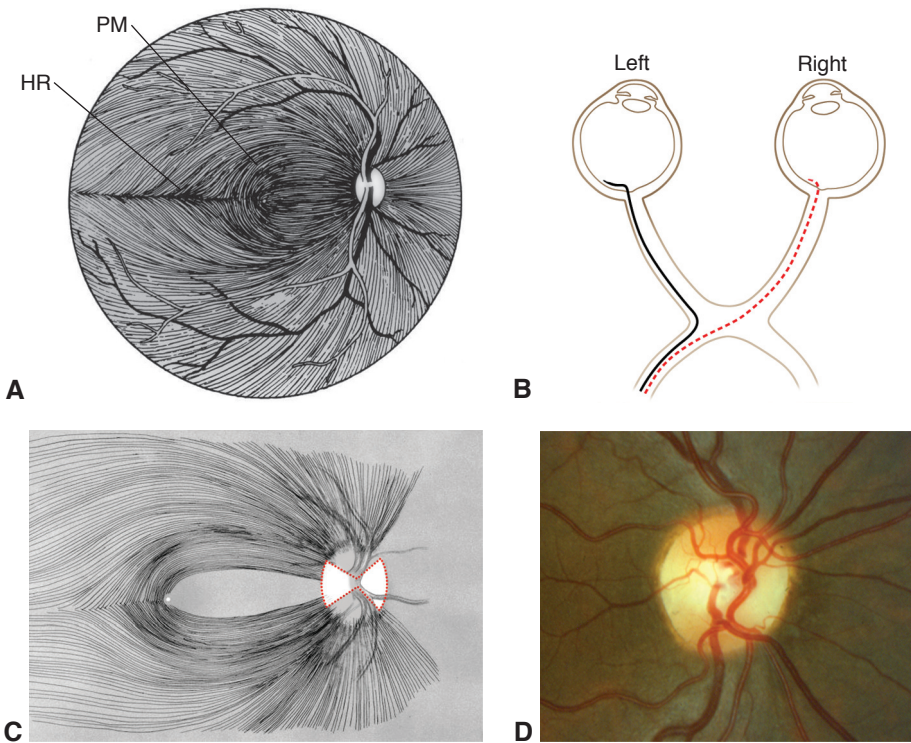


Figure 1-18 Anatomy of retinal ganglion cell axons in the retina and optic nerve. **A**, Pattern of the nerve fiber layer of axons from ganglion cells to the ONH. Superior, inferior, and nasal fibers take a fairly straight course. Temporal axons originate above and below the horizontal raphe (HR) and take an arching course to the ONH. Axons arising from ganglion cells in the nasal macula project directly to the ONH as the papillomacular bundle (PM). **B**, Lesions involving the decussating nasal retinal fibers (represented by the *dashed red line*) can result in bow-tie atrophy. **C**, Schematic depiction of damage to nasal and macular fibers of the retina and patterns of nasal and temporal optic nerve atrophy (represented by *red outlined triangles*) corresponding to damage to crossing nasal fibers. Therefore, band, or bow-tie, atrophy occurs with loss of nasal macular and peripheral fibers in the contralateral eye of a patient with a pregeniculate homonymous hemianopia or a bitemporal hemianopia. **D**, Clinical photograph of a right optic nerve demonstrating bow-tie atrophy. (Part A reprinted from Kline LB, Foroozan R, eds. *Optic Nerve Disorders*. 2nd ed. *Ophthalmology Monographs* 10. New York: Oxford University Press, in cooperation with the American Academy of Ophthalmology; 2007:5; part B illustration by Christine Galapp; part C courtesy of Neil Miller, MD; part D courtesy of Lanning Kline, MD.)

Optic Nerve

The optic nerve begins anatomically at the ONH but physiologically and functionally within the RGC layer that covers the entire retina. The first portion of the optic nerve, representing the confluence of approximately 1.0–1.2 million RGC axons, traverses the sclera through the lamina cribrosa, which contains approximately 200–300 channels. The combination of small channels and a unique blood supply (largely from branches of the posterior ciliary arteries) probably plays a role in several optic neuropathies. Axonal transport—both anterograde and retrograde—of molecules, subcellular organelles, and metabolic products occurs along the length of the optic nerve and is an energy-dependent system requiring high concentrations of oxygen. The anterograde axonal transport system can be subdivided into slow, intermediate, and fast speeds. The axonal transport system is sensitive to ischemic, inflammatory, and compressive processes.

Just posterior to the sclera, the optic nerve acquires a dural sheath that is contiguous with the periorbita of the optic canal and an arachnoid membrane that supports and protects the axons and is contiguous with the arachnoid of the subdural intracranial space through the optic canal. This arrangement permits free circulation of CSF around the optic nerve up to the ONH. Just posterior to the lamina cribrosa, the optic nerve also acquires a myelin coating, which increases its diameter to approximately 3 mm (6 mm including the optic nerve sheath) from the 1.5 mm of the ONH. The myelin investment is part of the membrane of oligodendrocytes that join the nerve posterior to the sclera.

The intraorbital optic nerve extends approximately 30 mm to the optic canal. The extra length of the intraorbital optic nerve allows unimpeded globe rotation as well as axial shifts within the orbit. The CRA and CRV travel within the anterior 10–12 mm of the optic nerve. The CRA supplies only a minor portion of the optic nerve circulation; most of the blood supply comes from pial branches of the surrounding meninges, which are in turn supplied by small branches of the OphA (see Fig 1-10). An approximate topographic representation is maintained in the optic nerve. Peripheral retinal receptors are found more peripherally, and the papillomacular bundle travels temporally and increasingly centrally within the nerve.

As the optic nerve enters the optic canal, its dural sheath fuses with the periorbita. It is also surrounded by the *annulus of Zinn*, which serves as the origin of the 4 rectus muscles and the superior oblique muscle. Within the canal, the optic nerve is accompanied by the OphA inferiorly and separated from the superior orbital fissure by the optic strut (the lateral aspect of the lesser wing of the sphenoid), which terminates superiorly as the anterior clinoid. Medially, the optic nerve is separated from the sphenoid sinus by bone that may be thin or dehiscent. The optic canal normally measures approximately 8–10 mm long and 5–7 mm wide but may be elongated and narrowed by processes that cause bone thickening (eg, fibrous dysplasia, intraosseous meningioma). The canal runs superiorly and medially. Within the canal, the optic nerve is relatively anchored and can easily be injured by shearing forces transmitted from blunt facial trauma (see Chapter 4).

At its intracranial passage, the optic nerve passes under a fold of dura (the falciform ligament) that may impinge on the nerve, especially if it is elevated by lesions arising from the bone of the sphenoid (tuberculum) or the sella. Once it becomes intracranial, the optic nerve no longer has a sheath. The anterior loop of the carotid artery usually lies just below

and temporal to the nerve, and the proximal ACA passes over the nerve. The gyrus rectus, the most inferior portion of the frontal lobe, lies above and parallel to the optic nerves. The 8–12 mm intracranial portion of the optic nerve continues to the optic chiasm.

Optic Chiasm

The optic chiasm measures approximately 12 mm wide, 8 mm long in the anteroposterior direction, and 4 mm thick (Fig 1-19). It is inclined at almost 45° and is supplied by small arterial branches from the proximal ACA and ACoA. The chiasm is located just anterior to the hypothalamus and the anterior third ventricle (forming part of its anterior wall and causing an invagination) and approximately 10 mm above the sella. The exact location of the chiasm with respect to the sella varies but is usually directly superior (Fig 1-20).

Within the chiasm, the fibers coming from the nasal retina (approximately 53% of total fibers) cross to the opposite side to join the corresponding contralateral fibers. The inferior fibers (those subserving the superior visual field) are the first to cross. The anterior loop of fibers into the contralateral optic nerve (Wilbrand knee) may be an artifact in

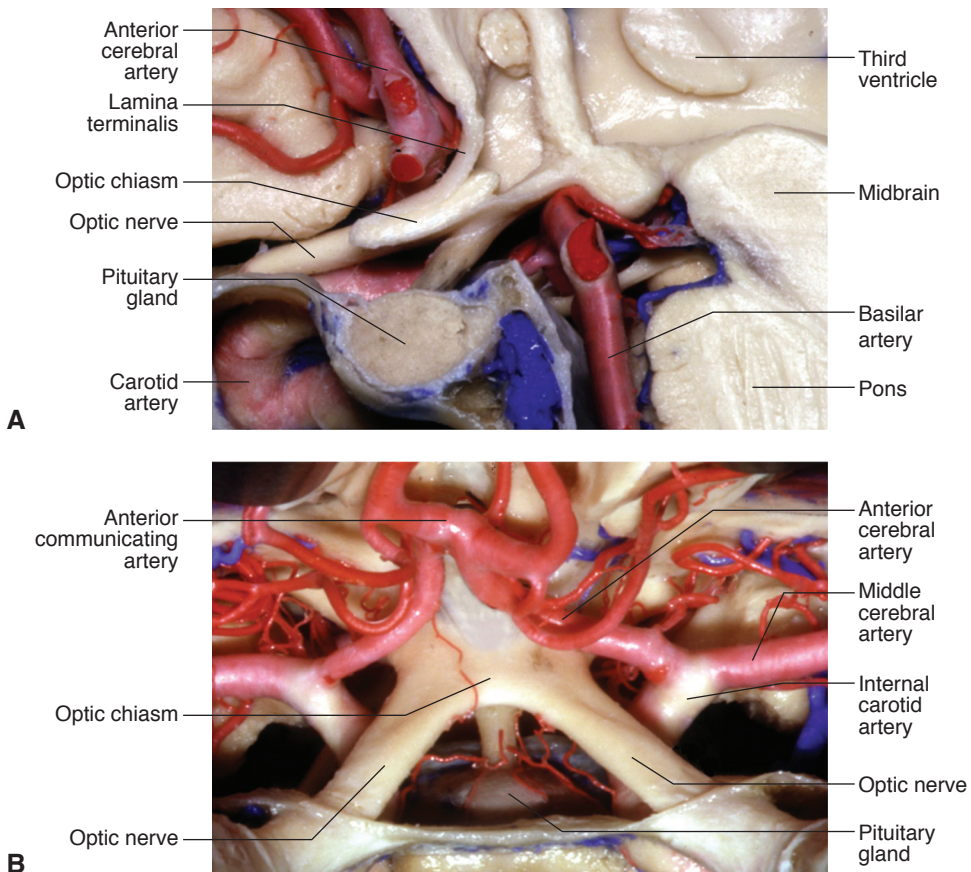


Figure 1-19 Anatomical dissection of the optic chiasm and surrounding structures. **A**, Sagittal view. **B**, Superior view. (Courtesy of Albert L. Rhoton Jr, MD.)

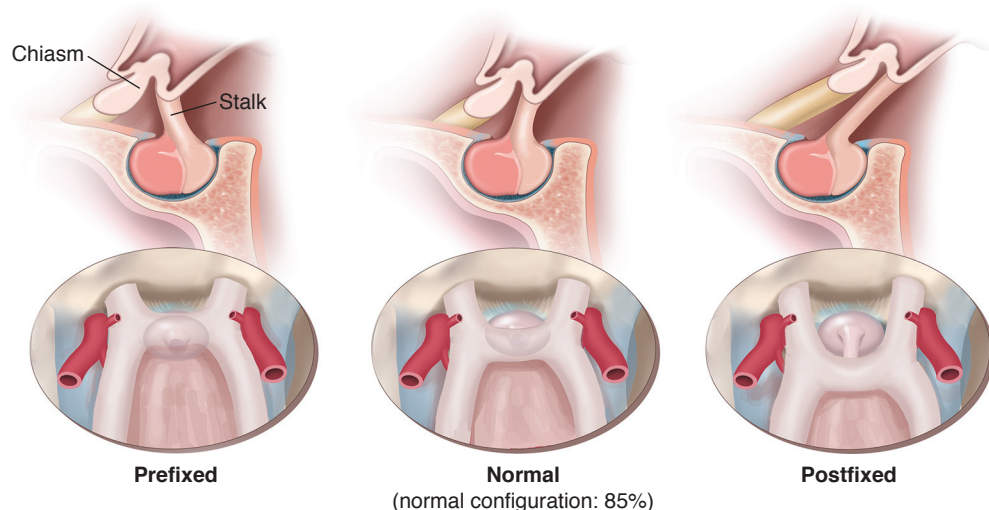


Figure 1-20 Position of the optic chiasm in relationship to the tuberculum sellae. (Illustration by Rob Flewell, CMI.)

monkeys, but not necessarily in humans. The finding of a superior temporal visual field defect contralateral to a central scotoma localizes the pathology to the junction of the optic nerve and chiasm. The macular fibers tend to cross posteriorly within the chiasm; this arrangement underlies the bitemporal scotomatous field defects observed with posterior chiasmatic compression.

Optic Tract

The fibers exiting from the chiasm proceed circumferentially around the diencephalon lateral to the hypothalamus and in contact with the ambient cistern (see Fig 1-11). Just prior to the LGN, the fibers involved in the pupillary pathways exit to the pretectal nuclei; other fibers exit to the superficial layers of the superior colliculi (SC) via the brachium of the SC. These fibers, which originate from ipRGCs, are likely the sole source of pupillomotor input from the retina to the midbrain. The ipRGCs also project to the supra-chiasmatic nucleus of the hypothalamus, which is probably responsible for light-induced diurnal rhythms.

The incongruous nature of optic tract visual field defects is explained by the lack of proximity between corresponding fibers from the right and left eyes. Most of the axons that originate in the retinal ganglion cells terminate within the LGN.

The LGN is located in the posterior thalamus below and lateral to the pulvinar and above the lateral recess of the ambient cistern. The LGN is a peaked, mushroom-shaped structure that is divided into 6 levels. The 4 superior levels are the termini of P-cell axons, which are the ganglion cells with smaller receptive fields; they are responsible for mediating maximal spatial resolution and color perception. The 2 inferior layers receive input from M-cell fibers, which are the ganglion cells with larger receptive fields; they are more sensitive to motion detection. Axons originating in the contralateral eye terminate in

layers 1, 4, and 6 of the LGN; the ipsilateral fibers innervate layers 2, 3, and 5. As the fibers approach the LGN, the superior fibers move superomedially and the inferior fibers swing inferolaterally. Overall, the retinal representation rotates almost 90°, with the superior fibers moving medially and the inferior fibers laterally. The macular fibers tend to move superolaterally. Cortical and subcortical pathways may modulate activity in the LGN. In addition, the cortex, SC, and pretectal nuclei project back to the LGN.

Cortex

Following a synapse in the LGN, the axons travel posteriorly as the optic radiations to terminate in the primary visual (calcarine) cortex in the occipital lobe (Fig 1-21). The most inferior of the fibers first travel anteriorly, then laterally and posteriorly to loop around the temporal horn of the lateral ventricles (called the Meyer loop) (see Fig 1-17). More superiorly, the fibers travel posteriorly through the deep white matter of the parietal lobe. The macular (central) fibers course laterally, with the peripheral fibers concentrated more at the superior and inferior aspects of the radiations. Injury to fibers within a radiation produces a homonymous hemianopia, a contralateral visual field defect that respects the vertical midline. If the corresponding fibers from the 2 eyes are close to each other, the field defect is identical in each eye, or congruous. Congruous field defects occur as a result of lesions involving the calcarine cortex. More anterior involvement often produces incongruous field defects, suggesting that the corresponding fibers lie farther apart more anteriorly in the visual pathways.

The *primary visual cortex* (known variously as *V1*, *striate cortex*, or *Brodmann area 17*) is arrayed along the horizontal calcarine fissure, which divides the medial surface of the

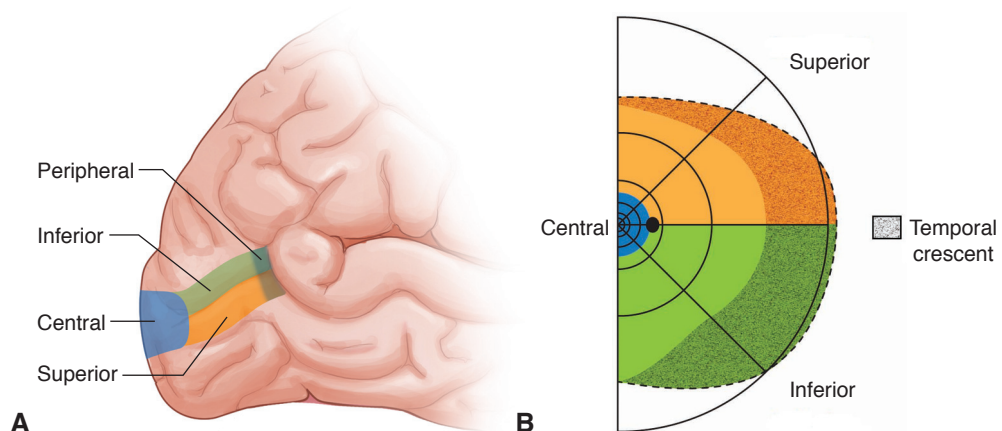


Figure 1-21 Primary visual cortex and corresponding visual field representation. **A**, Left occipital cortex showing the location of the striate cortex within the calcarine fissure. *Blue* represents the macula (central visual field); *green* represents the inferior visual field; and *orange* represents the superior visual field. The most peripheral fibers are represented by the *stippled colors*. **B**, Right hemifield, plotted with kinetic perimetry, corresponds to the regions of the striate cortex in **A**. The *stippled area* corresponds to the monocular temporal crescent, which is mapped in the most anterior ~8% of the striate cortex. (Illustrations by Christine Galapp.)

occipital lobe. Fibers of the optic radiations terminate in the fourth layer of the 6 layers of the primary visual cortex. The macular fibers terminate more posteriorly. Fibers from the most lateral (temporal crescent) visual field (originating only in the contralateral eye) terminate most anteriorly.

The cortex is heavily weighted to central retinal activity, with 50%–60% of the cortex responding to activity within the central 10° and approximately 80% of the cortex devoted to macular activity (within 30°). The superior portion of the cortex continues to receive information from the inferior visual field in a retinotopic distribution. This retinotopic mapping throughout the afferent visual pathways allows lesions to be localized based on visual field defects. In addition, the anteromedial portion of the striate cortex represents the far monocular temporal visual field of the contralateral eye (temporal crescent). Therefore, a far monocular temporal visual field defect localizes the lesion to the contralateral anterior occipital cortex (see Fig 1-21).

The *parastriate cortex* (also called V2, or *Brodmann area 18*) is contiguous with the primary visual cortex and receives its input from V1. Area V3 lies primarily in the posterior parietal lobe and also receives direct input from V1. Area V3 has no sharp histologic delineation from V2 and sends efferent information to the basal ganglia (pulvinar) and the midbrain. Cells in this area are thought to be able to respond to more than one stimulus dimension, suggesting that visual integration occurs in this region. Area V4, which is located within the lingual and fusiform gyrus, seems to be particularly sensitive to color. Damage to this area is probably responsible for most cases of cerebral achromatopsia. Anterior and lateral to area V4, V5 (posterior and within the superior temporal sulcus and gyrus subangularis) is very sensitive to movement and direction (Fig 1-22). The underlying white matter is heavily myelinated. Area V5, which corresponds to the

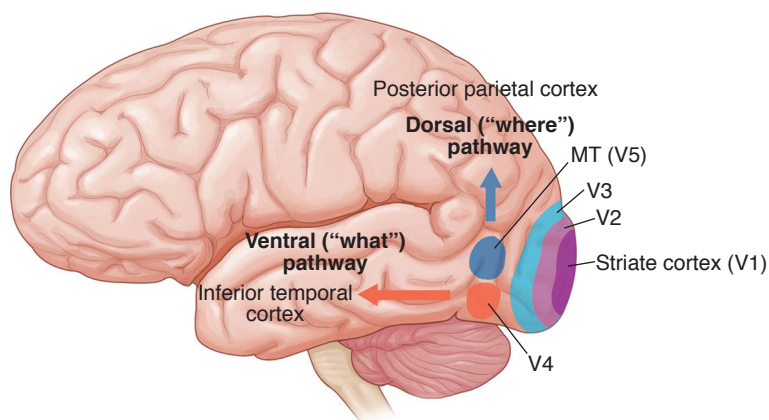


Figure 1-22 Parallel visual processing pathways in the human brain. The occipitotemporal (ventral, or "what") pathway begins in the striate cortex (V1) and projects to the angular gyrus for language processing, to the inferior temporal lobe for object identification, and to the limbic structures. The occipitoparietal (dorsal, or "where") pathway begins in the striate cortex and projects to the posterior parietal cortex and the superior temporal cortex, and is responsible for visual-spatial analysis. MT = medial temporal visual area.

medial temporal visual region, receives ipsilateral input from V1 and direct input from the M-cell layers of the LGN. The neurons in this area encode the speed and direction of moving stimuli. This sensory area is likely the origin of pursuit movements and thus connects the afferent and efferent pathways. The receptive fields of V5 are larger than those of V1. The SC receives afferent input both directly from the anterior visual pathways and indirectly from the calcarine cortex. The superficial layers contain a retinotopic map that overlies the deeper layers, which are primarily concerned with saccadic generation.

Horton JC, Hoyt WF. The representation of the visual field in human striate cortex. A revision of the classic Holmes map. *Arch Ophthalmol*. 1991;109(6):816–824.

Kardon R, Anderson SC, Damarjian TG, Grace EM, Stone E, Kawasaki A. Chromatic pupil responses: preferential activation of the melanopsin-mediated versus outer photoreceptor-mediated pupil light reflex. *Ophthalmology*. 2009;116(8):1564–1573.

Trobe JD. *The Neurology of Vision*. New York: Oxford University Press; 2001.

Efferent Visual System (Ocular Motor Pathways)

The anatomical, physiologic, and pathologic understanding of the ocular motor system has increased dramatically over the past decades due to results derived from primate model experiments, human electrophysiology testing, functional magnetic resonance imaging (fMRI) studies, and the clinical-pathologic-radiologic correlations of disorders in patients with documented eye movement abnormalities.

The ultimate purpose of the ocular motor system is to establish clear, stable, and binocular vision. Two basic human eye movements help perform these tasks:

1. gaze shift
2. gaze stabilization

These 2 movements can be further divided into 6 functional systems or classes (see the section Supranuclear Ocular Motor Systems: Function, Anatomy, Clinical Testing, and Disorders of Eye Movements in Chapter 8):

1. ocular fixation system
2. vestibular-ocular system
3. optokinetic system
4. saccadic system
5. smooth-pursuit system
6. vergence system

Each system appears to be under the control of—and modulated by—different regions of the brain (cortex) and brainstem, with considerable anatomical and functional overlap. This section provides an overview of the ocular motor system, with a detailed discussion of particularly clinically relevant structures. Interested readers can find a comprehensive description of the ocular motor system in the textbook *The Neurology of Eye Movements*

by Leigh and Zee. To facilitate learning, the discussion in this section follows a top-to-bottom approach:

- cortical control of eye movements, including frontal eye fields (FEFs), supplementary eye fields (SEFs), and posterior parietal cortex (PPC)
- subcortical centers, including basal ganglia (BG), thalamus, and SC
- brainstem or premotor coordination of conjugate eye movements, including coordination by the vestibular-ocular system and cerebellum
- ocular motor CNs (CNs III, IV, and VI)
- extraocular muscles (EOMs)

Leigh RJ, Zee DS. *The Neurology of Eye Movements*. 5th ed. Contemporary Neurology Series. New York: Oxford University Press; 2015.

Cortical Input

The efferent visual system spans a large segment of the central nervous system; many areas of the brain generate eye movements (Fig 1-23). Saccadic and smooth-pursuit eye movements were once thought to be derived from distinct supranuclear pathways; however, it now appears that these systems overlap considerably. In addition, there are 2 major visual pathways: one for the movement of images (magnocellular: M cells) and the other for discrimination of images (parvocellular: P cells).

Saccadic system

The cortical, or supranuclear, input for generating saccadic eye movements is divided into 2 parallel and interconnected descending pathways: (1) visually reflexive (parietal lobe) movements and (2) memory-guided and volitional (frontal lobe) movements. Visually guided movements require afferent system information either from the primary visual

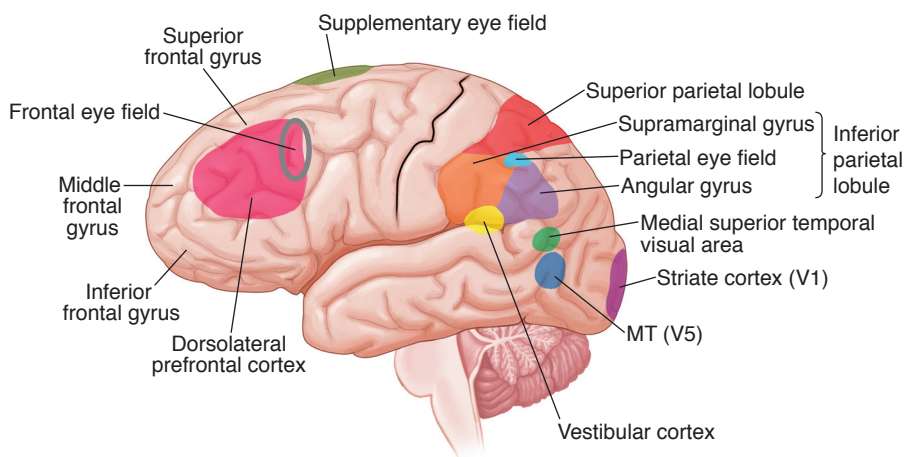


Figure 1-23 Overview of the cortical centers involved in the control of human eye movements. MT = medial temporal visual area. (Redrawn by Rob Flewell, CMI, with permission from Leigh RJ, Zee DS. *The Neurology of Eye Movements*. 4th ed. New York: Oxford University Press; 2006.)

system and cortex or from the accessory afferent system. The visually guided (to seen or remembered targets) and volitional saccadic supranuclear input comes largely from the FEFs, or *Brodmann area 8*. Cortical cells discharge prior to all voluntary and visually guided contralateral saccades. SEFs—located on the dorsomedial surface of the superior frontal gyrus—receive input from the FEFs and are responsible for programming saccades, particularly as part of learned behavior. In general, these cortical fibers project to the following structures in an organized framework:

- *subcortical structures*: BG, thalamus, and SC
- *brainstem neural network or premotor neurons*: several types of pontine neurons
- *brainstem saccade generators*: PPRF and rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF)
- *motoneurons of the ocular motor CNs*

Few cortical fibers project directly to the PPRF and riMLF. Cortical projections to the SC also arise from the PPC for visually guided reflexive saccades.

Smooth-pursuit system

The smooth-pursuit system for visual targets originates in area V5—the human homologue of the *medial temporal (MT)* visual area in the rhesus monkey—where it receives input from the primary visual system, both from the cortex (striate and extrastriate areas) and likely from magnocellular input directly from the LGN (Fig 1-24). The *medial superior temporal (MST)* area is also involved in generating pursuit signals in response to moving stimuli. The area appears to be supplied with information about head movement as well as eye movement commands (efference copy) and thus generates pursuit movements to follow a target while the head is moving. Target recognition and selection probably receive additional input through the reciprocal connections to the PPC. Information from the MT and MST projects via the posterior portion of the internal capsule to the *dorsolateral pontine nuclei (DLPN)* and lateral pontine nuclei. From these pontine nuclei, projections are sent to the cerebellum (paraflocculus and dorsal vermis), with outflow signals to the vestibular nuclei. The smooth-pursuit system is a double decussating pathway (the decussation occurs in both the pons and cerebellum); therefore, it can be simplistically considered an ipsilateral system.

For information on clinical disorders of the pursuit function, see Chapter 8 in this volume.

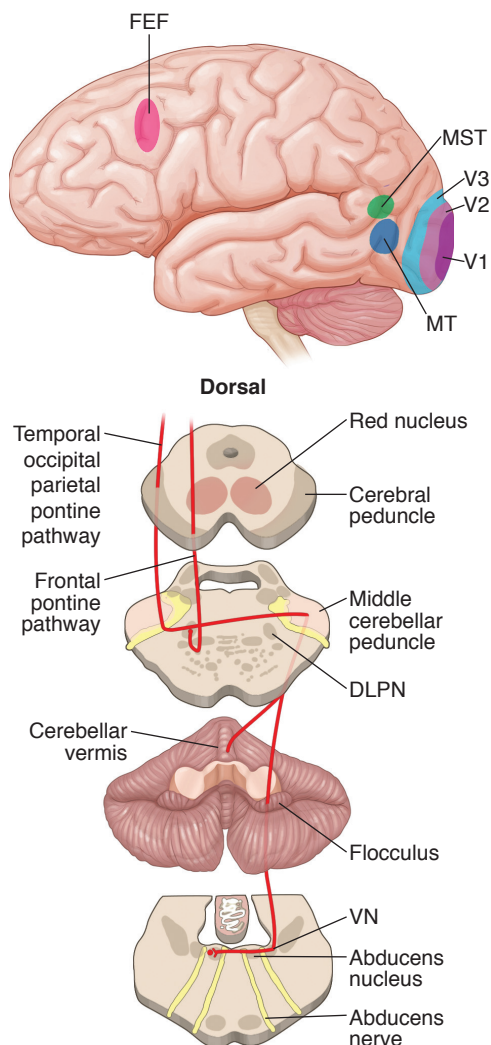
Subcortical Structures

The SC is divided into 2 parts: (1) superficial (dorsal) and (2) deep (ventral). The sensory signal (input from the visual cortex and retina) is processed mainly by the superficial SC. The motor signal originates within the deeper layers (the stratum griseum profundum and stratum album profundum) that receive position information from the more superficial layers. The SC projects contralaterally to multiple locations throughout the brainstem, including the DLPN.

Both the parietal and frontal lobe supranuclear pathways travel mainly to the SC; few fibers connect directly to brainstem premotor neurons. The supranuclear pathways

Figure 1-24 Pursuit system. A moving object creates signals in the striate cortex (V1), and from there to the extrastriate cortex (V2, V3). These signals are subsequently relayed to the middle temporal (MT) area and medial superior temporal (MST) areas, the posterior parietal cortex, and the frontal eye field (FEF). The descending cortical pathways of the temporal, parietal, and frontal lobes innervate the ipsilateral dorsal lateral pontine nucleus (DLPN). The neurons in the DLPN decussate and project to the vermis and flocculus in the contralateral cerebellar lobe, which innervates the medial vestibular nucleus (VN). VN neurons then decussate and project to the contralateral CN VI nucleus. The nucleus of CN VI initiates conjugate horizontal eye movements by innervating the ipsilateral lateral rectus muscle and, via internuclear neurons that travel in the medial longitudinal fasciculus, the contralateral medial rectus muscle.

(Illustration by Rob Flewell, CMI.)



also go through the BG (caudate nucleus, putamen nucleus, and substantia nigra pars reticulata). The BG appears to have several roles in the saccadic system, including inhibiting unnecessary reflexive saccades during fixation and helping control voluntary saccades.

The thalamus (internal medullary lamina and pulvinar) is involved in programming saccades. It receives information from the cortex and brainstem and projects only to the cortex and BG. Therefore, the thalamus appears to relay messages from the brainstem to the cortical eye fields.

Brainstem

The supranuclear pathways for saccades and smooth pursuit eventually reach the brainstem neural network (via the SC and BG), which allows for conjugate eye movements. The

following list of major anatomical structures and their functions helps set a foundation for discussion of the pathways for coordinating conjugate eye movements (Fig 1-25):

- *riMLF*: excitatory burst neurons that generate vertical and torsional saccades
- *interstitial nucleus of Cajal (INC)*: inhibitory burst neurons for vertical saccades and the neural integrator for vertical and torsional gaze
- *region of riMLF and INC*: inhibitory burst neurons for vertical and torsional saccades
- *posterior commissure (PC)*: projecting axons from the INC to the contralateral nuclei of CNs III, IV, and VI and the INC
- *medial longitudinal fasciculus (MLF)*: major pathway for relaying signals within the brainstem
- *DLPN*: neurons for smooth pursuit
- *nucleus prepositus hypoglossi (NPH)*: neural integrator for horizontal gaze
- *PPRF*: excitatory burst neurons that generate horizontal saccades and inhibitory burst neurons for horizontal saccades
- *CNs III, IV, and VI*: neurons that project directly to EOMs
- *vestibular nuclei (CN VIII)*: neurons that project to saccade generators and ocular motor CNs

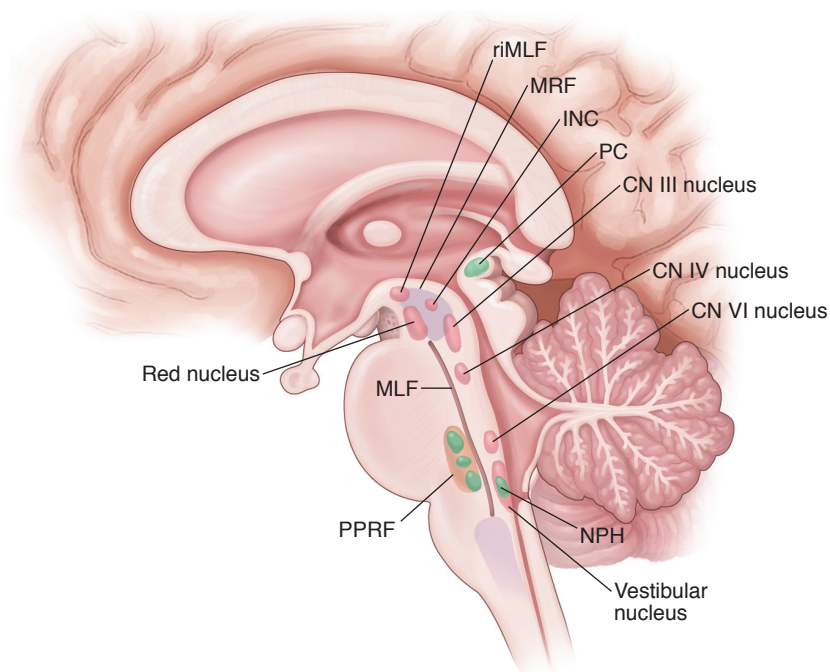


Figure 1-25 Schematic representation of a sagittal section of the brainstem showing the location of the important structures involved in eye movements. The *shaded areas* indicate the paramedian pontine reticular formation (PPRF). The DLPN are not visible because this illustration is a midsagittal section and the DLPN is laterally located; it is best visualized on an axial view through the rostral pons. INC = interstitial nucleus of Cajal; MLF = medial longitudinal fasciculus; MRF = mesencephalic reticular formation; NPH = nucleus prepositus hypoglossi; PC = posterior commissure; riMLF = rostral interstitial nucleus of MLF. (Illustration by Rob Flewell, CMI.)

In general, the midbrain is responsible for vertical eye movements and the pons for horizontal eye movements. Vertical and torsional saccades are generated from excitatory burst cells of the riMLF within the midbrain. In contrast, the pathways for vertical vestibular and vertical smooth pursuit ascend from the medulla and pons to the midbrain via the MLF. Horizontal saccades are generated from excitatory burst cells within the PPRF, and horizontal smooth-pursuit eye movements arise from the CN VI nucleus, which receives input from the vestibulocerebellum (see the section “Cerebellum,” later in this chapter).

Vertical gaze is controlled through the midbrain. The primary gaze center is located in the riMLF (Fig 1-26). This area receives input from the medial and superior vestibular nuclei via the MLF and other internuclear connections. Other areas in the rostral midbrain, including the INC, also modulate vertical motility. Burst-cell input may come in part from the PPRF caudally but also locally from within the riMLF. The INC (the neural integrator for vertical and torsional gaze) receives signals from the riMLF and from the vestibular nuclei and projects via the PC to the motoneurons of the CN III and CN IV

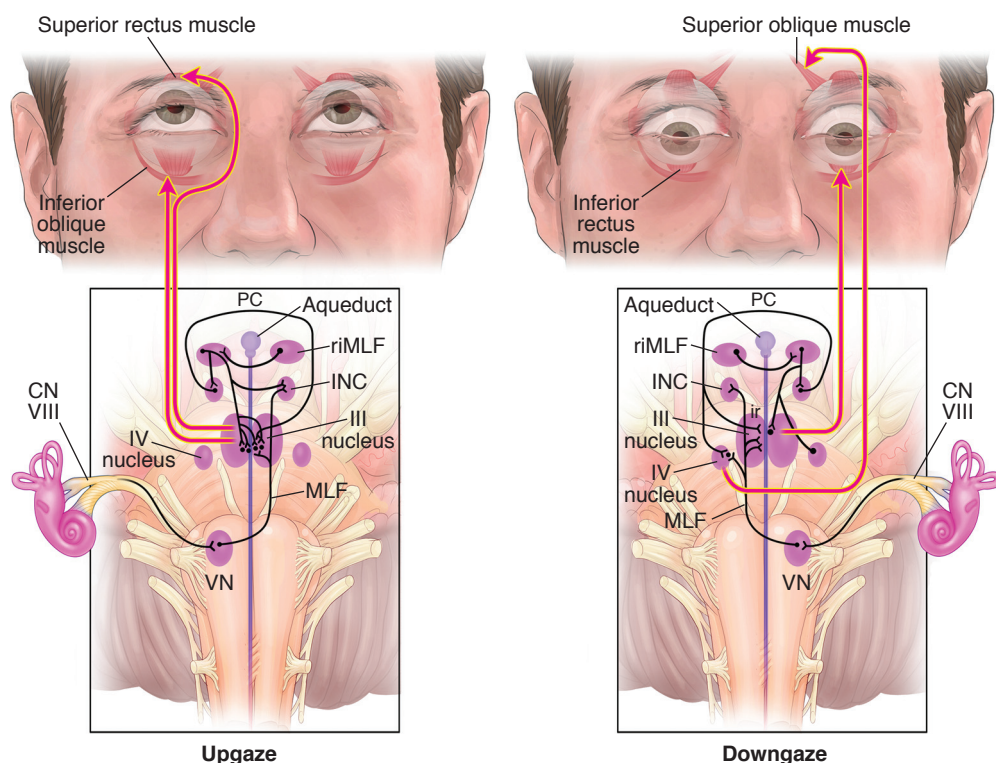


Figure 1-26 Anatomical schemes for the synthesis of upward and downward movements. From the vertical semicircular canals, primary afferents from CN VIII synapse on the VN and ascend into the medial longitudinal fasciculus (MLF) and brachium conjunctivum (not shown) to contact the CN III and CN IV nuclei and the interstitial nucleus of Cajal (INC). (For clarity, only excitatory vestibular projections are shown.) Excitatory burst neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) project to the motoneurons of CNs III and IV and send axon collaterals to the INC. Each riMLF neuron sends axon collaterals to yoke-pair muscles (Hering's law). III nucleus = oculomotor nerve (CN III) nucleus; IV nucleus = trochlear nerve (CN IV) nucleus; PC = posterior commissure. (Illustration by Rob Flewell, CMI.)

nuclei. Activity from the vertical gaze center is distributed to the CN III and CN IV nuclei. Information involved in upgaze crosses in the PC. Damage to this pathway results in dorsal midbrain syndrome, a disorder that includes vertical gaze difficulty (most commonly, impaired supraduction), skew deviation, light–near pupillary dissociation, eyelid retraction, and convergence-retraction nystagmus (see Chapter 9 in this volume).

Horizontal gaze is coordinated through the CN VI nucleus in the dorsal caudal pons (Fig 1-27). This nucleus receives tonic input from the contralateral horizontal semicircular canal through the medial and lateral vestibular nuclei. Burst information is supplied from the PPRF, which is directly adjacent to the CN VI nucleus and the MLF. The

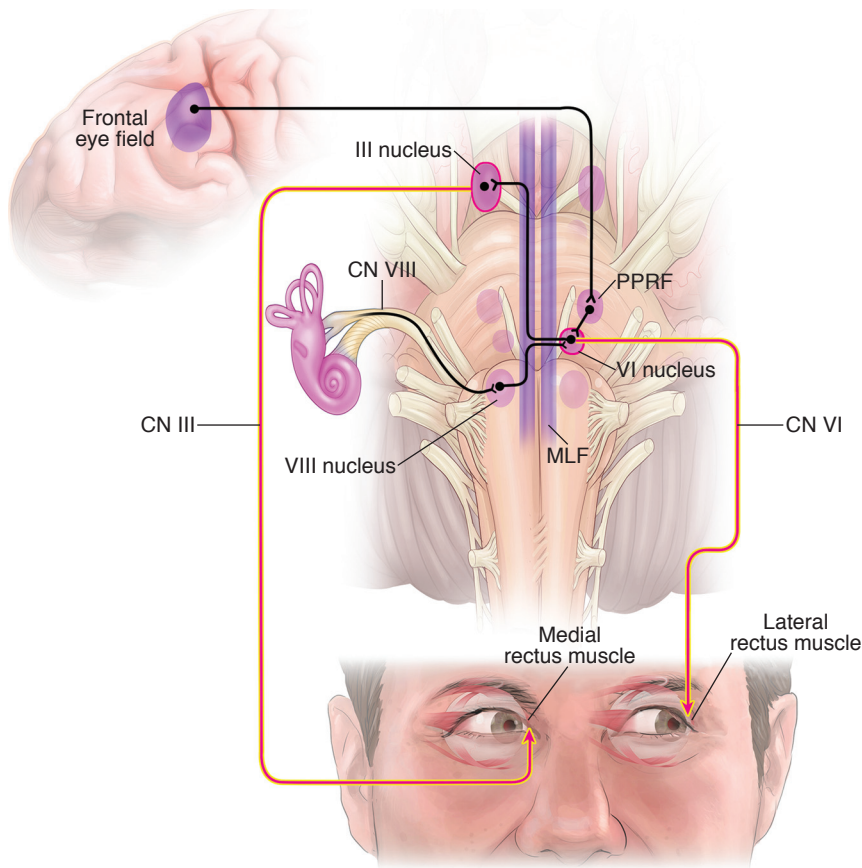


Figure 1-27 Anatomical scheme for the synthesis of signals for horizontal eye movements. From the horizontal semicircular canal, primary afferents of the vestibular nerve (CN VIII) project mainly to neurons of the vestibular nerve nucleus (CN VIII nucleus), which then send an excitatory connection to the contralateral abducens nucleus (CN VI nucleus). CN VI innervates the ipsilateral lateral rectus muscle and the contralateral oculomotor nerve nucleus (CN III nucleus) via the medial longitudinal fasciculus (MLF). Horizontal saccades are generated in the frontal eye field, which activates the contralateral PPRF. Burst neurons in the PPRF stimulate the ipsilateral abducens nucleus, with the subsequent pathway identical to that subserving horizontal vestibular-generated eye movements. Some neurons in the PPRF project to the nucleus prepositus hypoglossi (NPH) (the neural integrator) and then to the abducens nucleus.

(Illustration by Rob Flewell, CMI.)

burst cells are normally inhibited by omnipause neurons. Saccades are thought to be initiated by supranuclear inhibition of the omnipause cells, which allows burst-cell impulses to activate the horizontal and vertical gaze centers. To produce horizontal movement of both eyes, a signal to increase firing must be distributed to the ipsilateral lateral rectus and the contralateral medial rectus muscles. The lateral rectus muscle is supplied directly through ipsilateral CN VI. The contralateral medial rectus muscle is stimulated by interneurons that cross in the pons and ascend in the contralateral MLF. Therefore, pathology affecting the right MLF will result in a right *internuclear ophthalmoplegia*—a right (ipsilateral) adduction deficit with attempted left gaze—often accompanied by abducting nystagmus of the left (contralateral) eye and a skew deviation (see Chapter 7, Fig 7-5).

The distribution of infranuclear (ocular motor cranial nuclei and nerves) as well as supranuclear information requires internuclear communication within the brainstem. The most important of these pathways, the MLF, runs in 2 parallel columns from the spinal cord to an area of the midbrain PC that is located dorsomedial to the red nucleus and rostral to the INC. The bulk of the fibers contributing to the MLF originate in the vestibular nuclei. The projections from the superior vestibular nucleus are ipsilateral, and those from the medial vestibular nucleus are contralateral. The MLF also receives interneurons originating from the contralateral CN VI nucleus.

To maintain eccentric gaze, additional tonic input must be provided to the yoke muscles that hold the eye in position. This additional input is provided by integrating the velocity signal provided by the burst-neuron activity. For horizontal eye movements, integration takes place in the NPH, located adjacent to the medial vestibular nucleus at the pontomedullary junction, with input from the cerebellum. Neural integration for vertical eye movements involves the INC in addition to the cerebellum. Pathology affecting the neural integrator (often metabolic, associated with alcohol consumption or anticonvulsant medication) results in failure to maintain eccentric gaze, recognized clinically as gaze-evoked nystagmus (see Chapter 9).

Vestibular-ocular system

The output of the vestibular nuclei provides both the major supranuclear input into ocular motility and the major tonic input into eye position. This system has one of the shortest arcs in the nervous system, producing a fast response with extremely short latency. The hair cells of the semicircular canals alter their firing in response to relative movement of the endolymph (Fig 1-28). The signal is produced by a change in velocity (head acceleration) in any 1 of 3 axes. The information is then conveyed to the vestibular nuclei (located laterally in the rostral medulla) via the inferior and superior vestibular nerves. Hair cells in the macula acoustica of the utricle and saccule also contribute to the vestibular nerve. Calcium carbonate crystals within the otoliths respond to linear acceleration (most importantly, gravity) to orient the body. The vestibular nerve and the output of the membranous labyrinth (the cochlear nerve) make up the CN VIII complex and exit the petrous bone through the internal auditory meatus. CN VIII traverses the subarachnoid space within the cerebellopontine angle. Within the medulla, the vestibular information synapses in the medial, lateral, and superior vestibular nuclei. Tonic information from the horizontal canal crosses directly to the contralateral gaze center within the

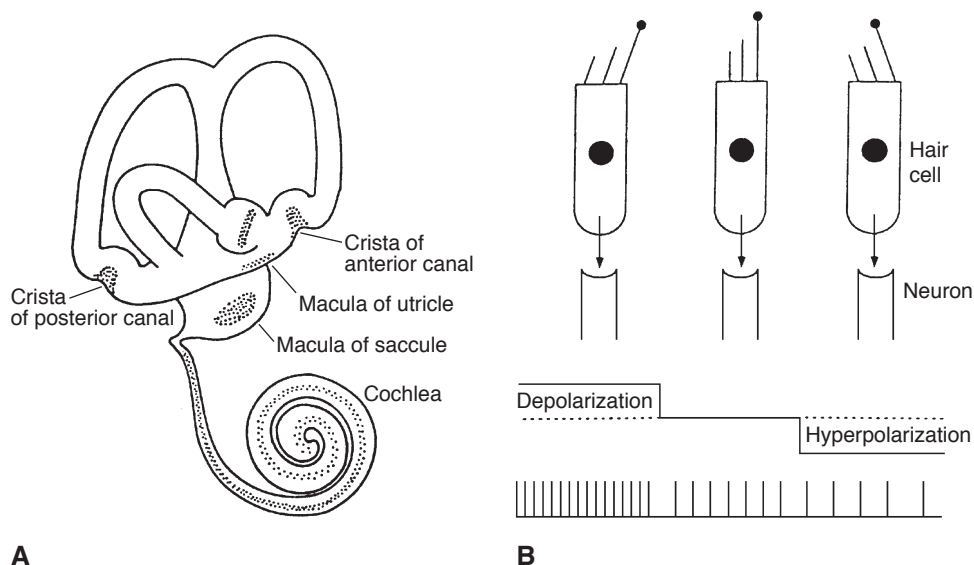


Figure 1-28 Vestibular system. **A**, Schematic of the mammalian labyrinth. The crista of the lateral semicircular canal is shown but not labeled (with the canal projecting forward). **B**, *Top*: Motion transduction by the vestibular hair cells. At rest, there is a resting rate of action potential discharge in the primary vestibular afferents (*center hair cell*). Depolarization occurs when the stereocilia are deflected toward the kinocilium (represented by the longest cilium, with a beaded end). Hyperpolarization occurs when the stereocilia are deflected away from the kinocilium. This movement of the stereocilia modulates the discharge rate in the vestibular nerve neuron. *Bottom*: The action potential generated by the shearing forces on the hair cell. Depolarization (*left side of graph*) causes an increase in the frequency of the action potential. Hyperpolarization causes a decrease in the frequency of action potential. (Reproduced with permission from Leigh RJ, Zee DS. *The Neurology of Eye Movements*. 4th ed. New York: Oxford University Press; 2006.)

CN VI nucleus in the dorsal medial aspect of the caudal pons just under the fourth ventricle. Tonic information from the anterior and posterior canals travels rostrally through several of the important internuclear connections to innervate the vertical gaze center in the rostral midbrain. Medial and inferior vestibular nuclei, as well as the NPH and the inferior olivary nucleus, project to the *nodulus* (a central nucleus of the cerebellum) and the *ventral uvula*. This pathway, which projects back to the vestibular nuclei, is responsible for the velocity storage mechanism (ie, the mechanism that maintains the vestibular signal beyond the output of the primary vestibular neurons).

For information on clinical disorders of vestibular-ocular function, see Chapter 8.

Cerebellum

The other major connection in the ocular motor system is to the *vestibulocerebellum*. The structures in this area, largely through the brachium conjunctivum, are responsible for adjusting the gain of all ocular movements. *Gain* may be defined as the output divided by the input. For example, keeping the eyes stable in space while the head rotates requires the eyes to move in a direction opposite that of head rotation at the same velocity and distance; this would be considered a gain of 1. The cerebellum is involved in gain adjustment to allow compensation after peripheral lesions (eg, vestibular nerve dysfunction

such as vestibular neuritis). Disease processes directly affecting the cerebellum may affect the vestibular-ocular reflex.

Efference copy information (regarding the position of the eyes) is supplied directly from the ocular motor pathways (possibly through cell groups of the paramedian tracts within the vestibular nuclei), whereas *afferent signal error* information arrives at the cerebellum via the climbing fibers from the inferior olivary nucleus. Additional cerebellar inputs include *mossy fiber input* from the vestibular nuclei and the NPH. Purkinje cells within the paraflocculus discharge during smooth pursuit. The dorsal vermis may play a role in initiating pursuit and saccades. The fastigial nucleus is responsible for overcoming a natural imbalance in the input from the vertically oriented semicircular canals. Thus, loss of fastigial function may be associated with development of downbeat nystagmus, as the imbalance in the vertical information causes constant updrift.

See Chapter 9 in this volume for further discussion of nystagmus and other spontaneous eye movement disorders.

Ocular Motor Cranial Nerves

Without neural activity, the visual axes are usually mildly to moderately divergent. The major tonic input to ocular motility is supplied by 3 pairs of ocular motor CNs—CNs III, IV, and VI—that innervate the 6 EOMs controlling ocular movement (Fig 1-29). In addition, CN III innervates the levator palpebrae superioris and the pupillary sphincter muscles.

Except for the inferior oblique muscle, the innervation to each of the EOMs occurs at approximately one-third of the distance from the apex. The inferior oblique muscle receives its innervation at approximately its midpoint from a neurovascular bundle running parallel to the lateral aspect of the inferior rectus muscle. All 6 EOMs receive their innervation on the inside surface, except for the superior oblique, where branches of CN IV terminate on the upper (outer) surface of the muscle.

See Chapter 7 for information on the clinical presentation of disorders due to infra-nuclear, fascicular, and peripheral ocular motor CN lesions.

Abducens nerve (sixth cranial nerve)

CN VI originates in the dorsal caudal pons just beneath the fourth ventricle. Its nucleus is surrounded by the looping fibers (genu) of CN VII and is adjacent to the PPRF and the

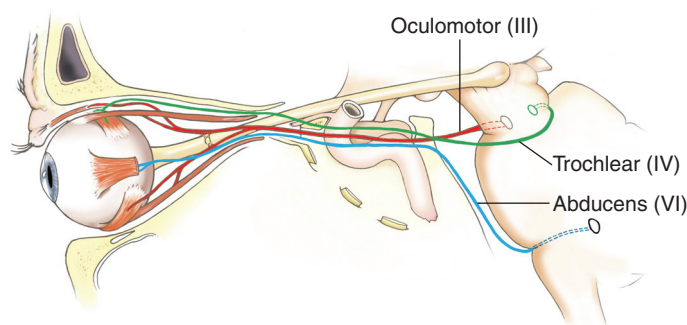


Figure 1-29 Lateral view of the course of CNs III, IV, and VI. (Illustration by Dave Peace.)

MLF (Fig 1-30). The CN VI nucleus contains primary motoneurons and interneurons that cross to the contralateral MLF to reach the CN III nucleus. Thus, pathology affecting the CN VI nucleus produces an ipsilateral gaze palsy. The motor axons exiting the CN VI nucleus (approximately 4000–6000 axons) travel ventrally and slightly laterally, medial to the superior olivary nucleus, to exit on the ventral surface of the caudal pons. As the fascicles pass through the brainstem, they lie adjacent to the spinal tract of CN V and traverse the corticobulbar tracts. Exiting the brainstem, the nerve runs rostrally within the subarachnoid space on the surface of the clivus from the area of the cerebellopontine angle to the posterior superior portion of the posterior fossa. The nerve pierces the dura approximately 1 cm below the petrous apex and travels beneath the petroclinoid ligament (Gruber ligament, which connects the petrous pyramid to the posterior clinoid) to enter the canal of Dorello. Within the canal, CN VI travels with the inferior petrosal sinus. Once it becomes extradural, the nerve is within the cavernous sinus (the only CN within the substance of the cavernous sinus), where it runs parallel to the horizontal segment of the carotid artery and CN V₁. It is also joined for a short segment by branches of the sympathetic chain lying within the wall of the intrapetrous carotid artery. Reaching the anterior portion of the cavernous sinus, CN VI traverses the superior orbital fissure (Fig 1-31) through the annulus of Zinn (see Fig 1-2C) to enter the medial surface of the lateral rectus muscle.

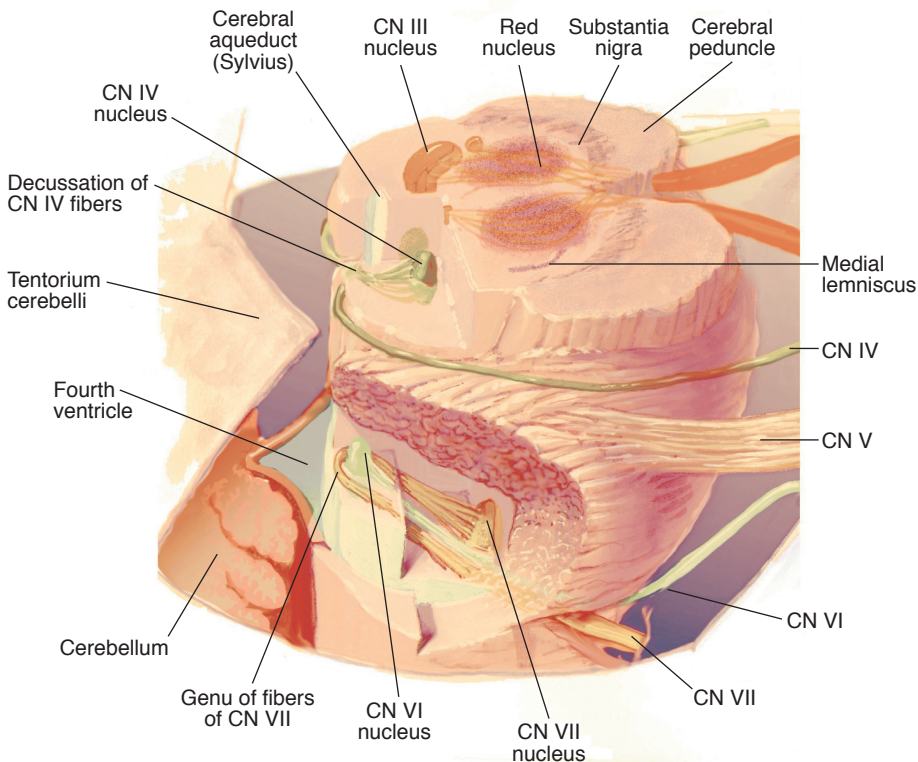


Figure 1-30 Intra-axial course of the ocular motor nerves at the level of the pons (*below*) and midbrain (*above*). Note the relationship to the surrounding cerebellum and CNs V and VII. (Illustration by Craig A. Luce.)

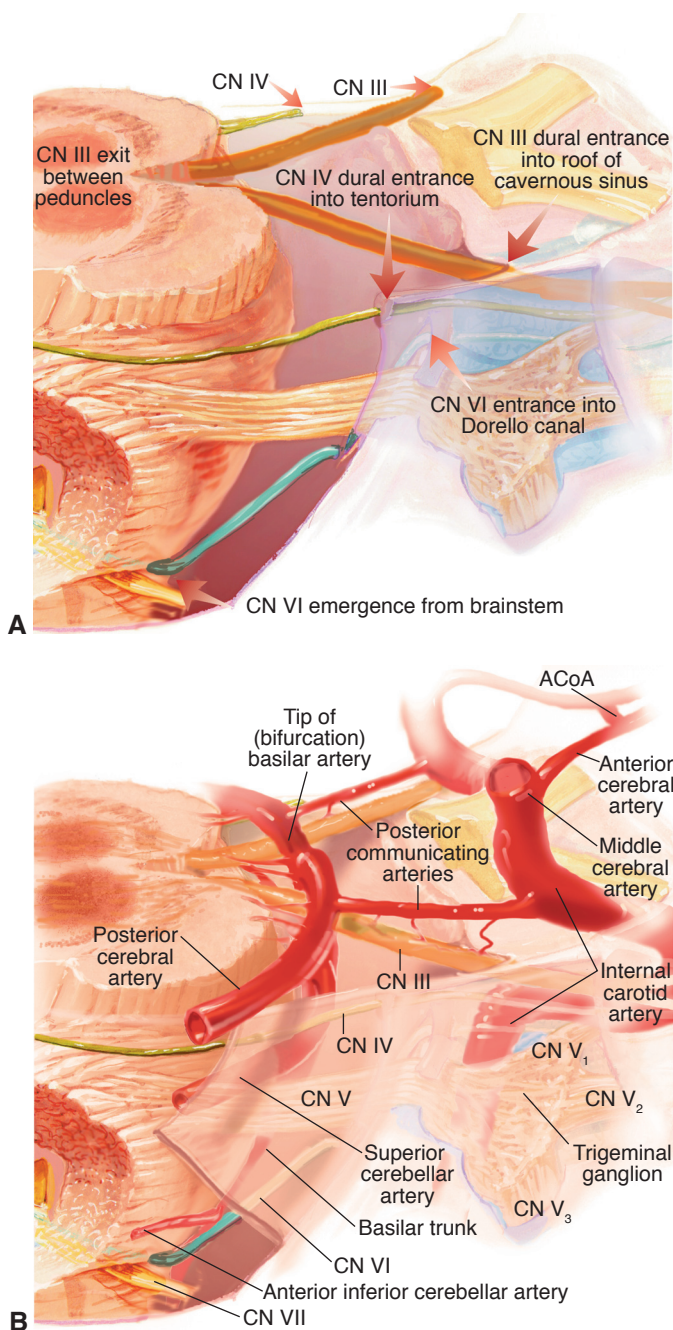


Figure 1-31 Anatomic relationships of the ocular motor nerves. **A**, Subarachnoid course of the ocular motor nerves. Note the relationship to the surrounding dural structures, particularly the tentorium and the dura of the clivus. The nerves enter dural canals at the posterior aspect of the cavernous sinus for CN III, at the tentorial edge for CN IV, and along the clivus for CN VI. **B**, Major blood vessels and their relationships to the ocular motor nerves. Note the passage of CN III between the superior cerebellar artery below and posterior cerebral artery above. CN VI runs by the anterior inferior cerebellar artery, which is a major branch off the basilar artery.

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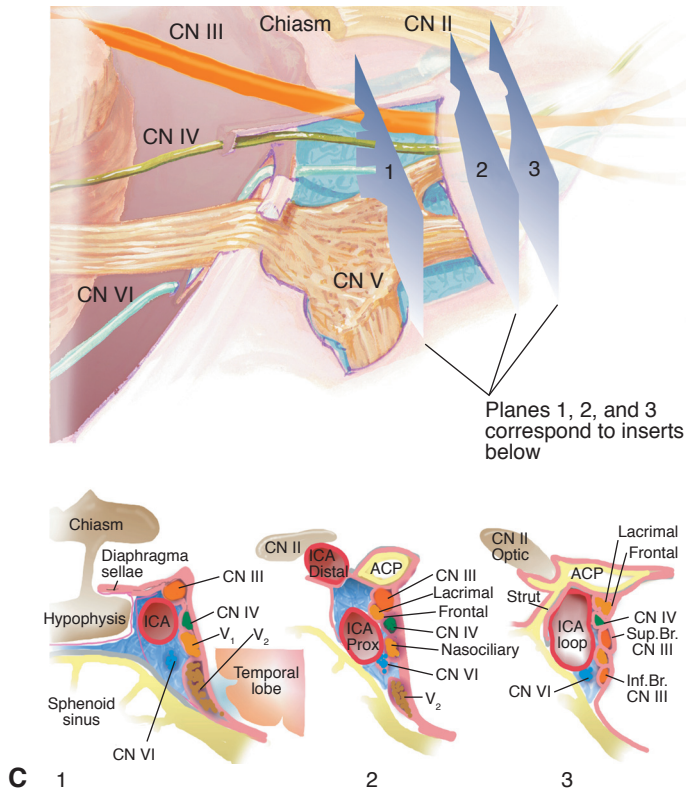


Figure 1-31 (continued) C, Intracavernous course of the ocular motor nerves. CNs III and IV run in the lateral wall of the cavernous sinus along with CN V divisions CN V₁ and CN V₂. CN VI runs in close approximation to the carotid artery within the cavernous sinus itself. As the nerves course toward the anterior aspect of the cavernous sinus and the superior orbital fissure, the ophthalmic branch of CN V (CN V₁) divides into 3 branches: the lacrimal, frontal, and nasociliary nerves. ACoA = anterior communicating artery; ACP = anterior clinoid process; ICA = internal carotid artery; Inf. Br. = inferior branch; Prox = proximal; Sup. Br. = superior branch. (Illustrations by Craig A. Luce.)

Trochlear nerve (fourth cranial nerve)

The CN IV nucleus lies within the gray matter in the dorsal aspect of the caudal mid-brain just below the aqueduct, directly contiguous with the more rostral CN III nucleus (see Fig 1-30). The intra-axial portion (fascicle) of CN IV is very short, running dorsally around the periaqueductal gray to cross within the anterior medullary vellum just caudal to the inferior colliculi and below the pineal gland. CN IV is the only CN that exits on the dorsal surface of the brainstem and has the longest unprotected intracranial course (which is probably responsible for its frequent involvement in closed-head trauma). Within the subarachnoid space, CN IV (which contains approximately 2000 fibers) swings around the midbrain, paralleling the tentorium just under the tentorial edge (where it is easily damaged during neurosurgical procedures that involve the tentorium).

CN IV enters the posterior lateral aspect of the cavernous sinus below the anterior tentorial insertion and underneath CN III. Covered by a variable sheath, CN IV runs forward within the lateral wall of the cavernous sinus. Anteriorly, CN IV crosses over CN III

to enter the superior orbital fissure outside and superior to the annulus of Zinn. CN IV crosses over the optic nerve to enter the superior oblique muscle within the superior medial orbit.

Oculomotor nerve (third cranial nerve)

The CN III nucleus is located dorsally within the midbrain beneath the aqueduct connecting the third and fourth ventricles (see Fig 1-30). The nuclear complex itself represents a collection of subnuclei that have specific identifiable functions (Fig 1-32). The fibers destined to innervate the levator palpebrae superioris, medial rectus, inferior rectus, pupil sphincter, and ciliary body muscles exit ventrally ipsilateral to the individual nuclei from which they originate. In contrast, the fibers from the superior rectus subnucleus, which lies along the midline, cross before exiting the brainstem to innervate the superior rectus muscle. Within the midbrain, CN III is topographically organized into a superior division (supplying the superior rectus and levator palpebrae superioris muscles) and an inferior division (supplying the medial and inferior rectus, inferior oblique, pupillary sphincter, and ciliary body muscles), but the true anatomical division into 2 branches occurs at the level of the anterior cavernous sinus/superior orbital fissure.

The fascicles of CN III traverse the ventral midbrain tegmentum, passing near and possibly through the red nucleus, the substantia nigra, and the corticospinal tracts within the cerebral peduncle. Numerous fascicles, totaling approximately 15,000 fibers, exit

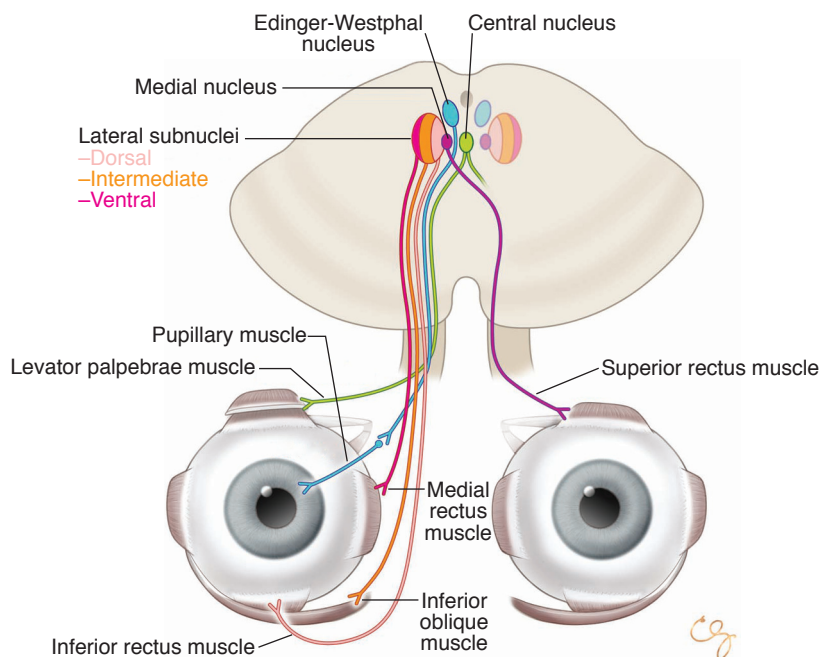


Figure 1-32 Oculomotor nucleus complex. Note that all extraocular muscles served by CN III are innervated by their respective ipsilateral nuclei except the superior rectus muscle. Parasympathetic fibers traveling to the pupillary sphincter muscle synapse in the ciliary ganglion in the orbit (see Fig 1-38). (Illustration by Christine Galapp.)

on the ventral surface of the peduncles. Although considered to be a single structure within the subarachnoid space, as is the case in the midbrain, the nerve and its various fibers are topographically organized. Within the subarachnoid space, the nerve passes between the SCA below and the PCA above. The nerve runs slightly oblique to the tentorial edge, parallel and lateral to the PCoA. The pupillary fibers are usually found on the dorsomedial surface of the nerve, where they are anatomically vulnerable to compression. The *uncus*, which is the most medial aspect of the temporal lobe, is located just above the tentorium and the subarachnoid portion of CN III. Unilateral supratentorial mass lesions may force the uncus through the tentorial notch (uncal herniation) to compress the ipsilateral CN III.

At the back edge of the dura of the clivus and cavernous sinus, the nerve enters its own dural canal just above CN IV. Running forward in the superior lateral wall of the cavernous sinus, the nerve separates into 2 divisions: (1) superior and (2) inferior. These divisions enter the orbit through the superior orbital fissure within the annulus of Zinn. The superior division runs forward intraconally to innervate first the superior rectus muscle and then the levator palpebrae superioris muscle. The inferior division sends parasympathetic fibers to the ciliary ganglion in the orbital apex approximately 10 mm anterior to the annulus of Zinn and lateral to the optic nerve. Within the ciliary ganglion, the fibers destined for the pupillary sphincter and the ciliary body synapse. The fibers subsequently accompany the branch destined for the inferior oblique muscle. There are approximately 9–10 times as many fibers associated with accommodation innervating the ciliary body as there are fibers reaching the pupillary sphincter muscle. This disparity may be one reason for the development of light–near dissociation in Adie tonic pupil (see Fig 10-6). The remaining branches of CN III within the orbit innervate the medial rectus and inferior rectus muscles.

Bhatti MT, Eisenschenk S, Roper SN, Guy JR. Superior divisional third cranial nerve paresis: clinical and anatomical observations of 2 unique cases. *Arch Neurol*. 2006;63(5):771–776.

Extraocular Muscles

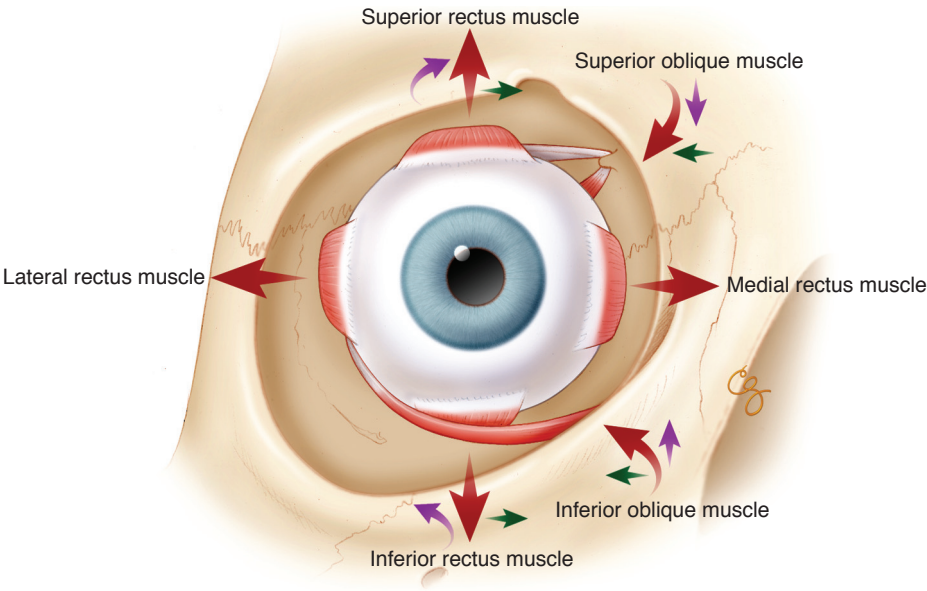
The final common pathways that influence the position of the eye within the orbit are the numerous soft-tissue elements connected to the globe. In addition to the EOMs, these tissues include the optic nerve, Tenon capsule, blood vessels, and the conjunctiva anteriorly. Orbital anatomy is discussed in BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*.

Of the 6 EOMs, 4 are *rectus muscles* (lateral, medial, superior, and inferior), and 2 are oblique (superior and inferior). The rectus muscles originate—along with the levator palpebrae superioris muscle—at the annulus of Zinn, a condensation of tissue around the optic nerve at the orbital apex. They run forward within sheaths that are connected by intermuscular septa to pierce the posterior Tenon capsule and insert on the anterior sclera, at points variably posterior to the corneal limbus, increasing from the medial through the inferior and lateral to the superior (*spiral of Tillaux*). The rectus muscles are also maintained in position by septal attachments to the orbital periosteum that act as pulleys.

The 2 *oblique muscles* insert on the posterior lateral aspect of the globe. The origin of the inferior oblique muscle is in the anteromedial periorbita near the posterior margin of the lacrimal fossa. The effective origin of the superior oblique muscle is the trochlea, a pulleylike structure located at the notch in the superior medial orbit. The superior oblique muscle runs anteriorly in the superior medial orbit to the trochlea, where its tendon reverses its direction of action.

The EOMs are of variable mass and cross section: The inferior oblique is the thinnest, and the medial rectus is the largest. Thus, with normal tonic innervation, the somewhat stronger medial rectus reduces the divergent phoria.

Each of the other muscles has primary, secondary, and tertiary functions that vary depending on the position of gaze (Fig 1-33). For further discussion and illustration of the EOMs and their actions, see BCSC Section 6, *Pediatric Ophthalmology and Strabismus*. Also see Chapter 7 in this volume for the clinical etiologies of EOM dysfunction.



<u>Muscle</u>	<u>Primary</u>	<u>Secondary</u>	<u>Tertiary</u>
Medial rectus	Adduction		
Lateral rectus	Abduction		
Inferior rectus	Depression	Extorsion	Adduction
Superior rectus	Elevation	Intorsion	Adduction
Inferior oblique	Extorsion	Elevation	Abduction
Superior oblique	Intorsion	Depression	Abduction

Figure 1-33 Primary, secondary, and tertiary functions of the extraocular muscles, right eye. (Illustration by Christine Gralapp.)

Sensory and Facial Motor Anatomy

Although the importance of CNs II, III, IV, and VI is obvious, CNs V and VII also contribute significantly to normal ophthalmic function and are frequently involved in neuro-ophthalmic disorders. For example, proper functioning of CN V is essential for prevention of corneal damage. In addition, complete loss of corneal sensation may be accompanied by abnormal corneal epithelial growth (neutrophic keratitis associated with loss of neural secreted growth factors).

Trigeminal Nerve (Fifth Cranial Nerve)

The sensory nerve terminates within the *trigeminal nucleus*. The nuclear complex of CN V extends from the midbrain to the cervical spinal cord and includes a main sensory nucleus, a mesencephalic nucleus, and a spinal nucleus (Fig 1-34). The *main sensory nucleus* is located within the pons lateral to the motor nucleus (the most rostral portion of the trigeminal complex except for the mesencephalic nucleus) and receives light-touch information from the skin of the face and the mucous membranes. The *mesencephalic nucleus* serves proprioception and deep sensation from the facial muscles, including the EOMs and the muscles involved in mastication (temporalis, pterygoid, and masseter). In addition, a *spinal nucleus* extends caudally to the level of the C4 vertebra, receiving pain and temperature information. The various sensory nuclei of CN V project to the contralateral thalamus and from there to the postcentral gyrus. The *motor nucleus* of CN V lies in the pons, medial to the sensory nucleus. The motor nucleus sends signals to the muscles

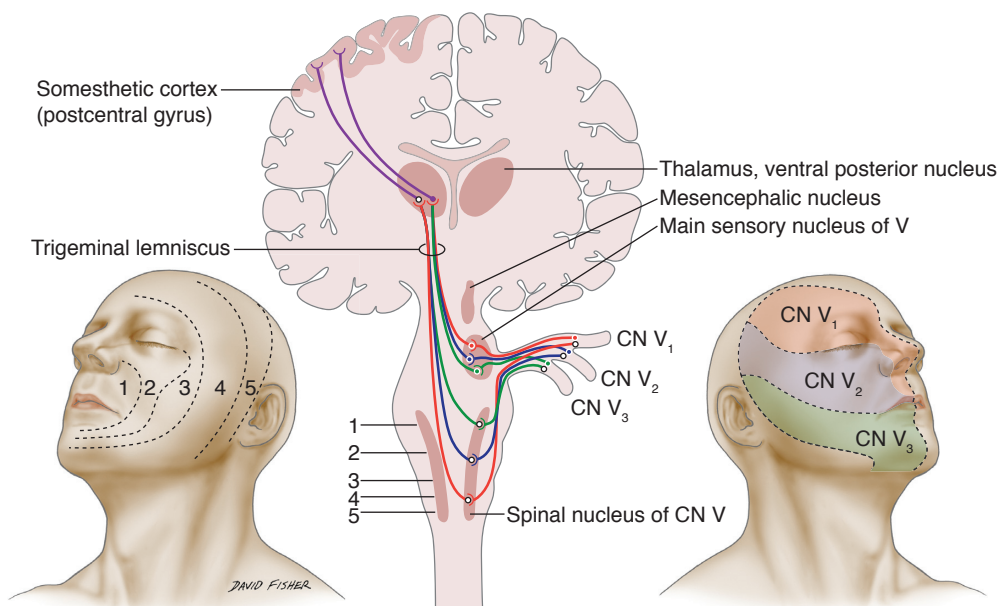


Figure 1-34 Diagram of the central pathways and peripheral innervation of CN V. (Used with permission from Kline LB. Neuro-Ophthalmology Review Manual. 6th ed. Thorofare, NJ: Slack; 2008:174, by David Fisher).

of mastication, the tensor tympani (which dampens sound by tensing the tympanic membrane within the middle ear as a reflex response to loud noises), the tensor veli palatini (which orients the uvula), the mylohyoid, and the anterior belly of the digastric muscle.

The fascicles of CN V enter the brainstem ventrally in the pons and extra-axially traverse the subarachnoid space to penetrate the dura just over the petrous pyramid. Within the subarachnoid space, the trigeminal root often comes in contact with the SCA. This proximity may be a cause of trigeminal neuralgia (atypical facial pain, discussed in Chapter 12) and is the anatomical basis for microvascular decompression. The 3 divisions of CN V synapse in the trigeminal (gasserian) ganglion (Fig 1-35), located in an extradural space at the floor of the middle cranial fossa (Meckel cave).

The *ophthalmic division* (CN V₁) is the most anterior branch of CN V exiting the trigeminal ganglion. It runs forward within the lateral wall of the cavernous sinus just below CN IV. As it approaches the superior orbital fissure extradurally, it divides into 3 major branches: (1) lacrimal, (2) frontal, and (3) nasociliary. In addition, small branches innervate the dura of the anterior middle cranial fossa, including the cavernous sinus, the parasellar region, the tentorium, and the dura of the petrous apex. These branches also innervate the floor of the anterior cranial fossa, including the falx cerebri and the major blood vessels at the skull base.

The lacrimal and frontal nerves enter the orbital apex outside the annulus of Zinn. At its terminus, the frontal nerve divides into supraorbital and supratrochlear branches, which innervate the forehead, frontal sinus, and upper eyelid (including the conjunctiva). The lacrimal nerve also runs anteriorly in the superior lateral orbit just above the lateral rectus to innervate the lacrimal gland and the skin just superotemporal to the orbit. The nasociliary branch is the only branch that enters the intraconal space through the annulus of Zinn. The nasociliary branch runs through the ciliary ganglion and anteriorly to innervate the globe through the short and long posterior ciliary nerves. Prior to reaching the globe, branches from the nasociliary division pass through the anterior and posterior ethmoidal foramina to innervate part of the ethmoidal sinuses, the lateral wall of the nose, and the skin of the nose to the nasal tip. This co-innervation of the globe and the nasal

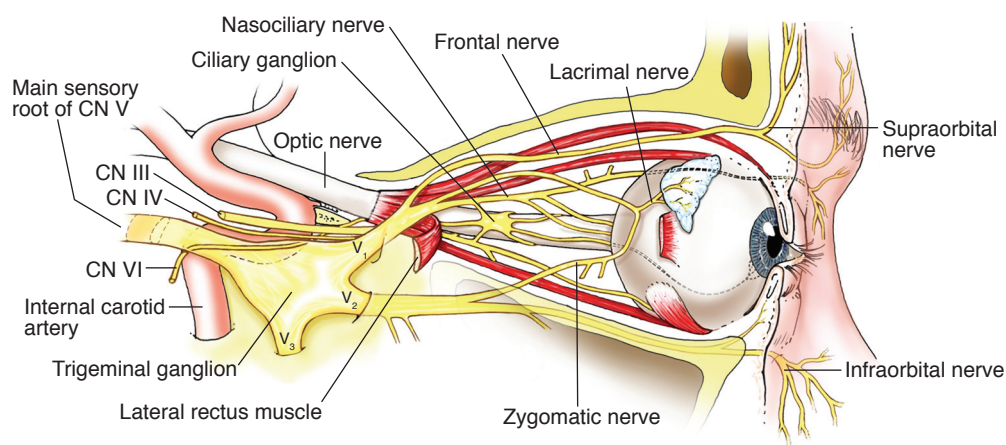


Figure 1-35 Lateral view of the orbit, showing its sensory nerves. (Illustration by Dave Peace.)

skin is the reason behind the development of Hutchinson sign (vesicles on the tip or side of nose) in patients with zoster ophthalmicus.

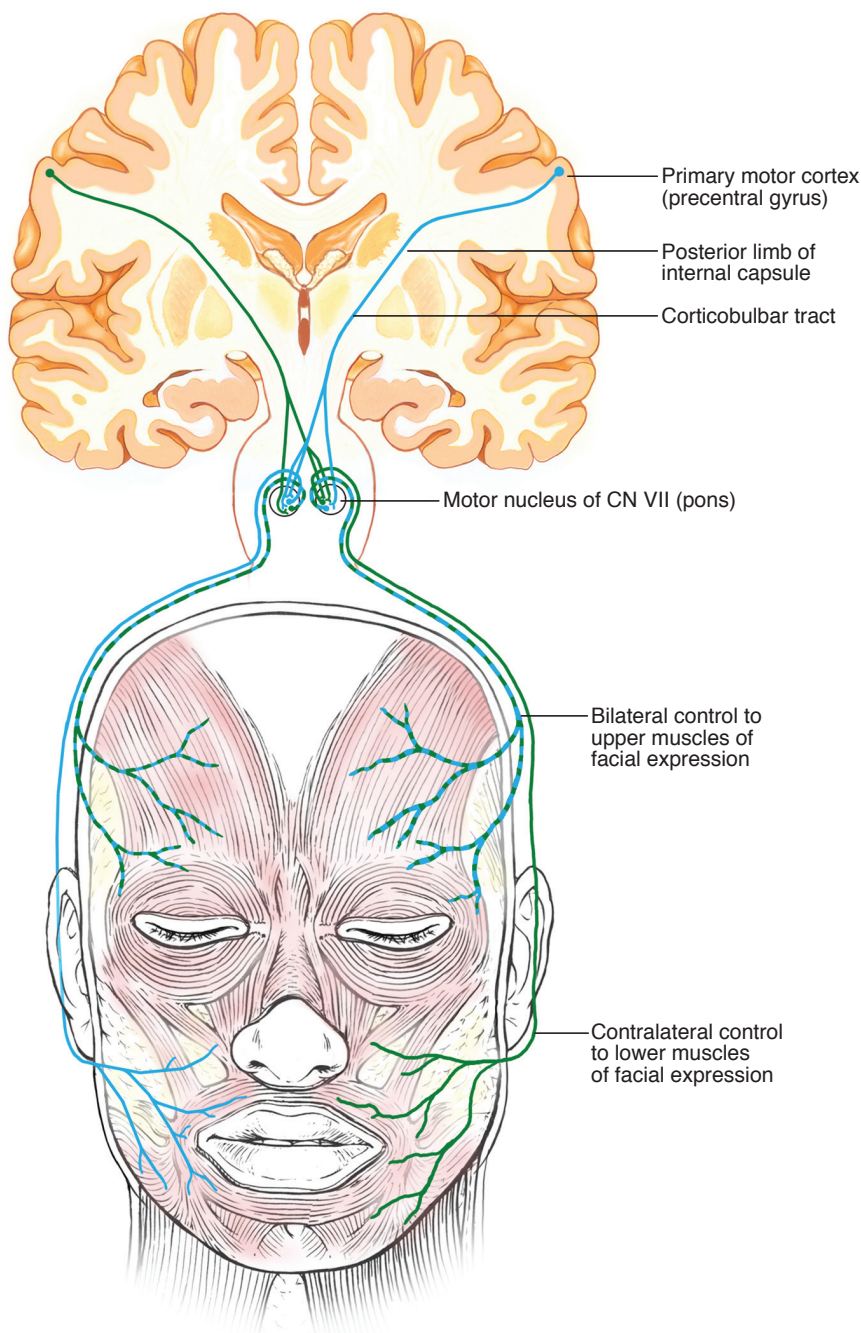
The *maxillary division* (CN V₂) runs forward at the inferior lateral base of the cavernous sinus to enter the foramen rotundum, located just below the superior orbital fissure. Before entering the canal, CN V₂ gives off the middle meningeal nerve, which supplies the dura of the lateral middle cranial fossa. On the anterior end of the foramen rotundum, CN V₂ enters the pterygomaxillary area. Two large pterygopalatine nerves supply sensation to the nasopharynx, hard and soft palate, and portions of the nasal cavity. Posterior alveolar nerves supply sensation to the upper gums and molars. The zygomatic nerve enters the orbit through the inferior orbital fissure and divides into the zygomaticofacial and the zygomaticotemporal nerves, which supply sensation to the lateral face (see Fig 1-35). The maxillary nerve continues anteriorly within a canal between the orbit above and the maxillary sinus below to exit through the infraorbital foramen (as the infraorbital nerve) just below the inferior orbital rim. It subsequently divides into palpebral, nasal, and labial branches. The maxillary division provides sensation to the cheek as well as the lower eyelid and upper teeth and gums.

The *mandibular division* (CN V₃) enters through the foramen ovale, lateral to the foramen lacerum and medial to the foramen spinosum (carrying the MMA). CN V₃ innervates the skin of the jaw and carries the motor division of CN V to the muscles of mastication and neck. Motor paralysis results in contralateral deviation of the jaw when it is closed (due to weakness of the ipsilateral temporalis) and ipsilateral deviation when protruded (due to weakness in the lateral pterygoid).

Facial Nerve (Seventh Cranial Nerve)

CN VII is responsible for the movement of the facial muscles. Voluntary facial movements, along with other motor activity, originate in the *precentral gyrus*. White-matter tracts pass through the internal capsule and cerebral peduncles along with the other corticobulbar fibers. The motoneurons destined for the upper face receive information from both sides (bilateral innervation), whereas the lower facial musculature receives information only from the contralateral cortex (Fig 1-36). The CN VII nucleus receives additional information from BG extrapyramidal connections, which are largely responsible for involuntary blinking. Abnormal blinking, as present in BG disorders such as Parkinson disease, is probably mediated through alterations in inhibition of the supranuclear control of the blink reflex.

The motor fibers of the CN VII nucleus originate in the tegmentum of the caudal pons, ventrolateral to the CN VI nucleus and medial to the spinal nucleus of CN V. The dorsal subnucleus receives bilateral innervation and supplies the upper face; the lateral subnucleus (contralateral innervation) supplies the lower face. The fascicles of CN VII pass dorsomedially to surround the CN VI nucleus, creating a bump on the floor of the fourth ventricle (the genu of CN VII intra-axially and the colliculus of CN VII on the floor of the fourth ventricle). CN VII exits the ventrolateral surface of the pons along with fascicles of the nervus intermedius, which contains the facial nerve sensory fibers and the visceral efferent fibers (see the section Parasympathetic Pathways later in this chapter). The subarachnoid portion of the nerve runs anteriorly and laterally to enter the internal auditory meatus along with CN VIII.



A

Figure 1-36 Supranuclear, nuclear, and infranuclear anatomy of the facial nerve (CN VII). **A**, The corticobulbar fibers travel through the internal capsule down into the medial one-third of the corticospinal tracts in the cerebral peduncles of the midbrain. The pathways for the upper one-third of facial function (brow and orbicularis muscles) run parallel to but apparently distinct from the pathways for the lower two-thirds along the pyramidal tracts. The corticobulbar fibers travel in the basis pontis; those that control the lower facial muscles decussate at the level of the pons to synapse on the contralateral CN VII nucleus. Corticobulbar fibers that control the upper facial muscles decussate to synapse on the contralateral CN VII nucleus, and some of the fibers do not cross, reaching the ipsilateral CN VII nucleus.

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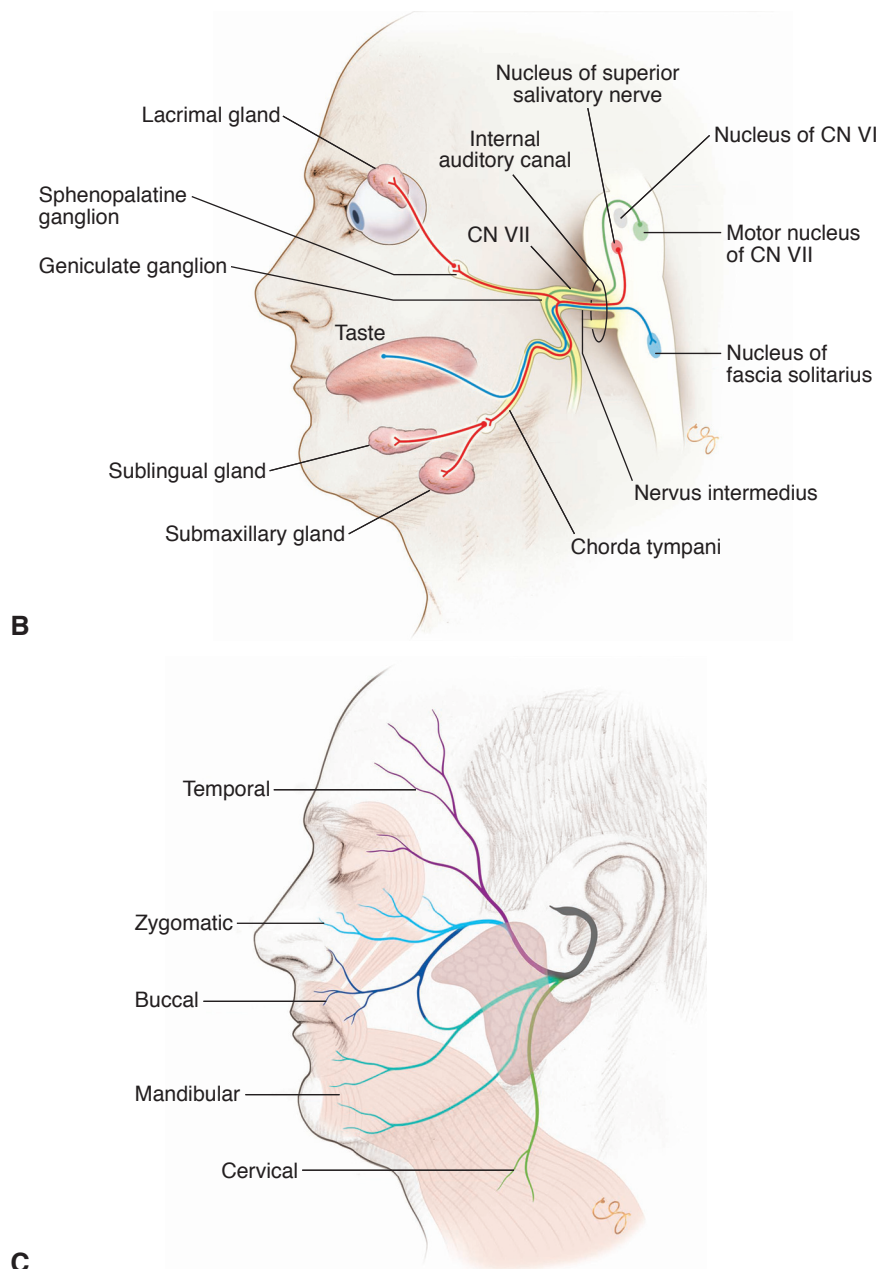


Figure 1-36 (continued) B, CN VII is predominantly motor in function, with its nucleus located in the caudal pons. CN VII courses dorsomedially and encircles the nucleus of CN VI. After bending around the CN VI nucleus, CN VII exits the pons in the cerebellopontine angle close to CNs V, VI, and VIII. CN VIII, the motor root of CN VII, and the nervus intermedius (the sensory and parasympathetic root of CN VII) enter the internal auditory meatus. Sensory cells located in the geniculate ganglion continue distally as the chorda tympani nerve, which carries taste fibers. Peripheral fibers of the nervus intermedius portion of CN VII initiate salivary, lacrimal, and mucous secretion. **C,** After emerging from the parotid gland, CN VII innervates the muscles of facial expression via 5 peripheral branches. (Part A reproduced with permission from Bhatti MT, Shiffman JS, Pass AF, Tang RA. Neuro-ophthalmologic complications and manifestations of upper and lower motor neuron facial paresis. *Curr Neurol Neurosci Rep.* 2010;10(6):448–458; part A illustration by Dave Peace; parts B, C illustrations by Christine Gralapp.)

Within the petrous bone, CN VII enters the fallopian canal and traverses 3 segments (the labyrinthine, the tympanic, and the mastoid) that run in close proximity to the semi-circular canals. The parasympathetic fibers destined for the lacrimal gland separate from CN VII in the region of the geniculate ganglion to accompany the greater superficial petrosal nerve. The stapedial nerve exits to innervate the stapedius muscle, and the chorda tympani conducts parasympathetic innervation to the submaxillary gland and afferent fibers from the anterior two-thirds of the tongue. These special afferent fibers are responsible for taste in the anterior tongue and synapse in the geniculate ganglion.

The main branch of CN VII exits the stylomastoid foramen just behind the styloid process at the base of the mastoid. The extracranial trunk of the nerve passes between the superficial and deep lobes of the parotid gland, where it divides into 2 trunks: (1) the temporofacial superiorly and (2) the smaller cervicofacial inferiorly. These variably divide into 5 major sub-branches: (1) temporal, (2) zygomatic, (3) buccal, (4) mandibular, and (5) cervical. The temporal and zygomatic branches laterally innervate the orbicularis oculi muscles. The infraorbital and buccal branches may also variably contribute to the inferior orbicularis.

Eyelids

The muscles of the eyelids are divided into 2 components: (1) orbital (responsible for forced closure) and (2) palpebral. The palpebral muscles are further separated into pretarsal (predominantly intermediate fast-twitch fibers responsible for normal blinks) and preseptal muscles. This separation occurs at the upper eyelid fold, located approximately 6–7 mm above the eyelid margin. The superior eyelid fold is formed by collateral insertion of the levator aponeurosis to the skin of the eyelid. Closure of the eyelids is marked by an increase in activity of the orbicularis muscle and inhibition of the levator palpebrae superioris muscle. The balance of tonic orbicularis and active levator activity determines the amount of eyelid opening. For discussion of eyelid abnormalities encountered in neuro-ophthalmic practice, see Chapter 11. For further discussion of eyelid anatomy, including illustrations, see BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*.

Ocular Autonomic Pathways

Branches of the parasympathetic system play a role in lacrimal function, and pupil size is controlled by a balance between the innervation of the sympathetic fibers to the iris dilator muscles and of the parasympathetic fibers to the sphincter muscles. The accessory retractor muscles, including the Müller muscle in the upper eyelid, receive sympathetic innervation.

Sympathetic Pathways

Sympathetic activity originates in the posterolateral region of the hypothalamus. Activity in the hypothalamus is influenced by signals in the frontal, sensorimotor, and occipital cortex and in the limbic system (cingulate gyrus). The course of sympathetic fibers destined for the orbit is divided into first-, second-, and third-order segments (Fig 1-37).

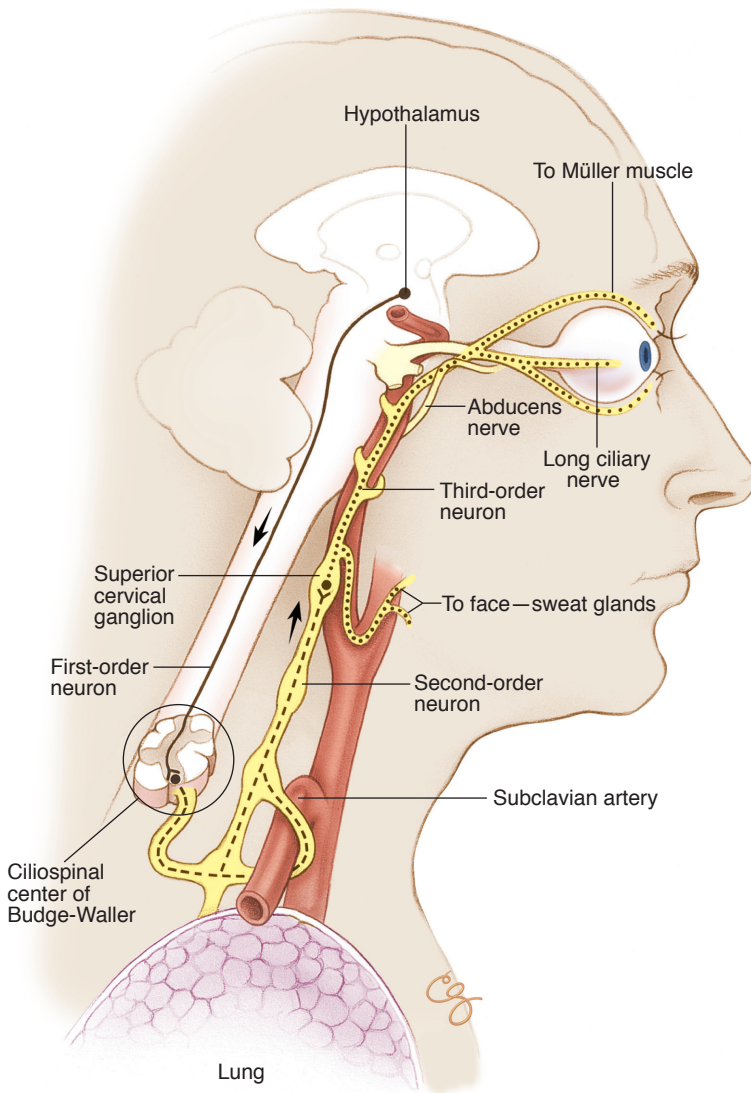


Figure 1-37 Anatomy of the sympathetic pathway showing first-order central neuron, second-order intermediate neuron, and third-order neuron pathways. Note the proximity of the pulmonary apex to the sympathetic chain. Note also the intimate relationship of the sympathetic fibers to CN VI within the cavernous sinus. (Illustration by Christine Gralapp.)

Axons destined for the dilator muscles of the pupil and Müller muscle descend as the first-order segment, along with other sympathetic fibers, superficially in the anteromedial column through the brainstem to the spinal cord. Within the cervical spinal cord, the sympathetic fibers continue in the intermediolateral column. From levels C8 to T2, the sympathetic fibers destined for the orbit synapse in the ciliospinal center of Budge-Waller.

The postsynaptic second-order fibers leave the spinal cord through the ventral rami of the cervical (C8) and upper thoracic (T1 and T2) levels before joining the paravertebral sympathetic plexus. Ascending rostrally, the sympathetic chain passes in the anterior loop

of the ansa subclavia proximate to the innominate artery on the right and the subclavian artery on the left just above the lung apex. These fibers pass through the inferior and middle cervical ganglia to terminate in the superior cervical ganglion, at the level of the angle of the jaw (C2) and the carotid artery bifurcation.

The postganglionic third-order fibers continue in the wall of the bifurcated carotid. Sympathetic fibers innervating the sweat glands of the lower face follow the ECA.

The sympathetic fibers destined for the pupil continue along the ICA, entering the cranium through the carotid canal. Some sympathetic fibers leave the carotid artery as it exits the petrous bone, combining with the greater superficial petrosal nerve to form the *vidian nerve*. These sympathetic fibers parallel the parasympathetic fibers to the lacrimal gland. Within the cavernous sinus, sympathetic fibers destined for the dilator muscles leave the carotid in conjunction with CN VI for a few millimeters. Further anteriorly in the cavernous sinus, the sympathetic fibers join the nasociliary branch of CN V₁. In the orbital apex, the fibers then pass through the ciliary ganglion (without synapsing). Along with the nasociliary branch, the sympathetic fibers reach the globe and travel with the long ciliary nerves to the dilator muscles of the pupil. The dilator muscle lies just superficial to the posterior pigment epithelium of the iris, which continues peripherally as the nonpigmented superficial layer of the ciliary body. The myoepithelial cells measure approximately 12.5 μm in thickness, with an apical epithelial portion and a basilar muscular portion that is oriented radially toward the pupillary opening. The muscular processes terminate peripheral to the sphincter muscle. Peripherally at the iris root, these cells are continuous with the pigmented epithelium of the ciliary body.

The fibers destined for the Müller muscle travel along the OphA and its subsequent frontal and lacrimal branches. The Müller muscle originates near the origin of the levator aponeurosis and inserts 10–12 mm inferiorly on the superior border of the tarsus. The superior orbital sympathetic fibers also innervate the sweat glands of the forehead. Thus, disruption of these sympathetic fibers is responsible for the mild ptosis and the frontal anhidrosis associated with distal Horner syndrome.

Parasympathetic Pathways

Parasympathetic activity originates in various areas within the brainstem. The fibers that control the pupil sphincter muscles originate in the Edinger-Westphal (EW) nuclei of the CN III nuclear complex within the midbrain. The main input to the EW nuclei is from the pretectal nuclei, both directly and via the PC. The pretectal nuclei, in turn, receive input directly from the afferent visual pathways via the pupillary tract, which leaves the optic tract in the brachium of the SC just anterior to the LGN (Fig 1-38). The cortex (especially the frontal lobes), the hypothalamus, and the reticular activating system provide tonic inhibitory signals to the EW nucleus. During sleep, the pupil becomes smaller through loss of this inhibitory activity. In addition, the EW nucleus receives input from the more ventral and rostral midbrain, probably related to bitemporal image disparity that serves as a stimulus for convergence and the near reflex.

The parasympathetic fibers and the CN III fascicles leave the CN III nucleus and exit in the interpeduncular fossa. Within the subarachnoid space, the parasympathetic fibers tend to run on the medial superficial surface of CN III. When CN III bifurcates in the

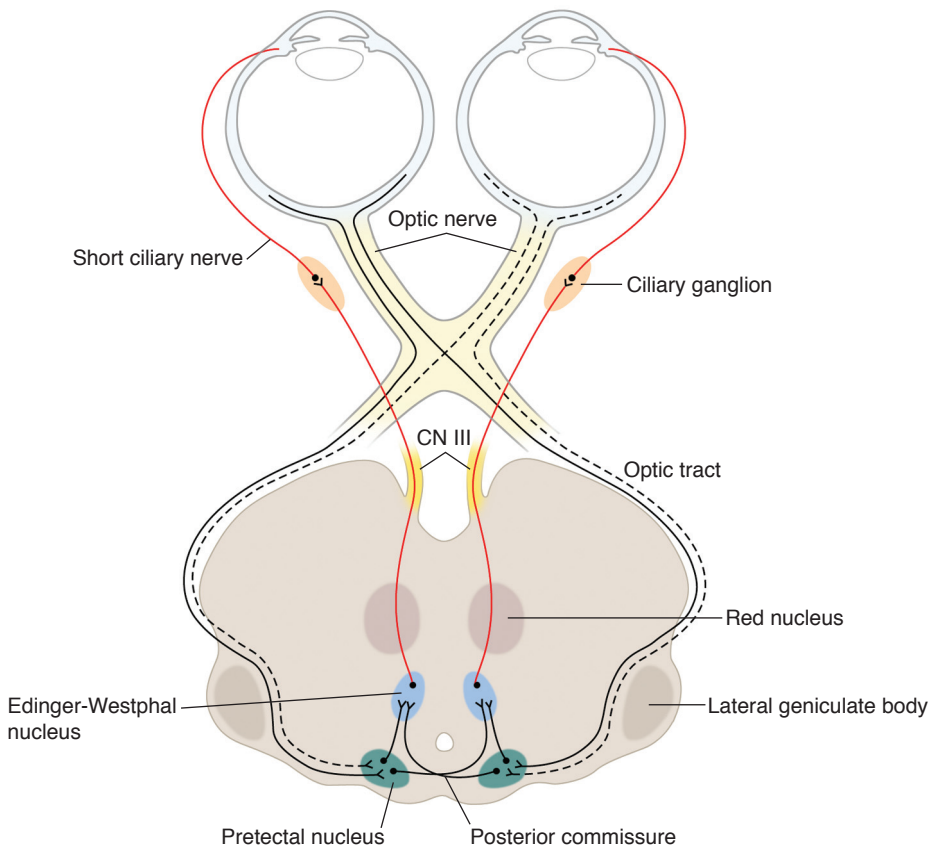


Figure 1-38 Pathway of the pupillary reaction to light. (Illustration by Christine Gralapp.)

anterior cavernous sinus, the parasympathetic fibers travel with the inferior division. In the orbital apex, these fibers synapse in the ciliary ganglion (as opposed to the oculosympathetic and nasociliary fibers, which travel through the ganglion without synapse). The postsynaptic fibers then travel with the branch destined for the inferior oblique muscle, joining the posterior ciliary nerves to reach the anterior segment and the iris sphincter muscles. The sphincter muscle measures approximately 0.8 mm in diameter and 0.15 mm in thickness. It travels circumferentially around the pupillary margin just anterior to the posterior pigmented epithelium and central to the termination of the dilator muscle cells. The muscle itself is made up of units composed of groups of 5–8 muscle cells.

Parasympathetic innervation to the lacrimal gland originates in the superior salivatory (salivary) nucleus located in the caudal pons posterolateral to the motor nucleus of CN VII. This nucleus receives sensory input from CN V and additional afferent fibers from the hypothalamus. Efferent parasympathetic fibers for lacrimal, mucous, and salivary secretion exit the nucleus, joining other parasympathetic efferent fibers coming from the salivatory nucleus and running with afferent gustatory fibers from the anterior two-thirds of the tongue in the nervus intermedius. The gustatory fibers synapse in the nucleus of the tractus solitarius parallel to the fascicles of CN VII in the nervus

intermedius (see Fig 1-36B). This nerve joins with CN VII to exit the brainstem on its ventral surface of the pontomedullary junction. Together with the other fascicles of CN VII, the parasympathetic fibers of the nervus intermedius run laterally to the internal auditory meatus. Within the petrous bone and fallopian canal, the parasympathetic fibers exit at the geniculate ganglion and then travel superficially over the petrous bone with the greater superficial petrosal nerve. This course parallels that of the ICA. In the area where the ICA turns to rise into the cavernous sinus, the fibers join the vidian nerve, which then travels through the sphenoid bone parallel to and beneath the foramen rotundum to enter the pterygomaxillary space. The fibers synapse in the sphenopalatine ganglion. The postganglionic fibers travel superiorly through the inferior orbital fissure and then with the lacrimal nerve to reach the lacrimal gland. The parasympathetic fibers are responsible for reflex tearing.

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Neuroimaging in Neuro-Ophthalmology

Introduction

Neuroimaging is an excellent diagnostic and prognostic tool in ophthalmology. However, it should be used in conjunction with, not as a substitute for, a detailed clinical evaluation of the patient. Prior to selecting an appropriate neuroimaging technique, the ophthalmologist should address the following clinical questions:

- What is the clinical presentation?
- Where is the lesion resulting in the clinical presentation?
- What are the potential etiologies of the lesion?

The choice of imaging modality and the timing of the study should be based on the differential diagnosis, nature of the suspected lesion (eg, vascular), location of the lesion, patient characteristics (eg, age, weight, allergies, comorbidities such as renal function, claustrophobia, presence of metallic foreign bodies or devices such as a pacemaker), and the availability of the desired imaging modality. The ophthalmologist should communicate directly with the neuroradiologist when selecting the best imaging modality and interpreting the neuroimaging study. Errors that the clinician might make when either ordering or reviewing a neuroimaging study fall into 2 broad categories: (1) prescriptive and (2) descriptive. *Prescriptive errors* include the following:

- failure to apply a dedicated study
- inappropriate use of a dedicated study
- omission of intravenous contrast material
- omission of specialized sequences

Interpretive errors include the following:

- failure to detect a lesion due to misleading clinical information
- rejection of a clinical diagnosis because an expected imaging abnormality is absent
- the assumption that a striking imaging abnormality accounts for the clinical abnormality
- failure to consider the lack of clinical specificity of an imaging abnormality

This chapter primarily discusses the 2 most common neuroimaging techniques used in neuro-ophthalmology clinical practice: (1) *computed tomography (CT)* (Fig 2-1) and (2) *magnetic resonance imaging (MRI)* (Fig 2-2). In general, most neuro-ophthalmic diseases are best assessed with MRI of the brain and/or orbits using contrast and fat-saturation techniques. If a vascular abnormality is suspected, *magnetic resonance angiography (MRA)* or *magnetic resonance venography (MRV)* can be added to the MRI; *computed tomography angiography (CTA)* or *computed tomography venography (CTV)* can be added to the CT.

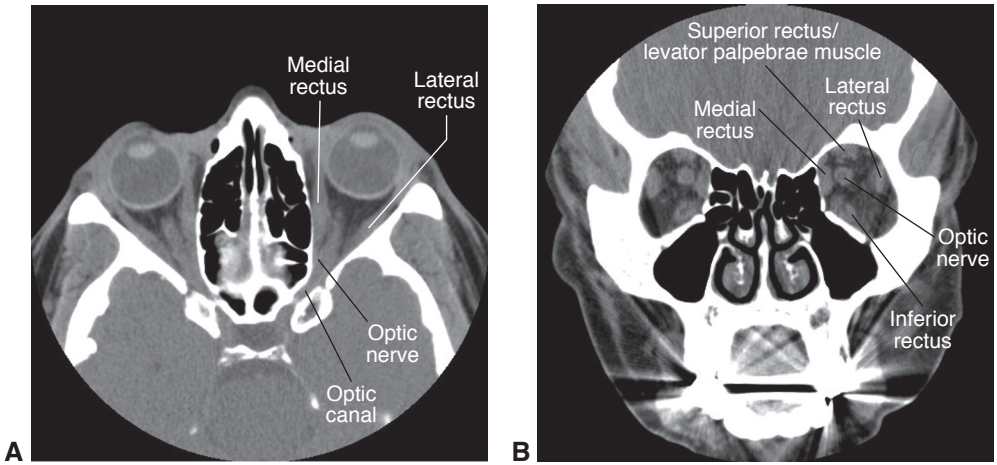


Figure 2-1 Computed tomography (CT) scans. Axial (A) and coronal (B) orbital views of a healthy subject. (Courtesy of Rod Foroozan, MD.)

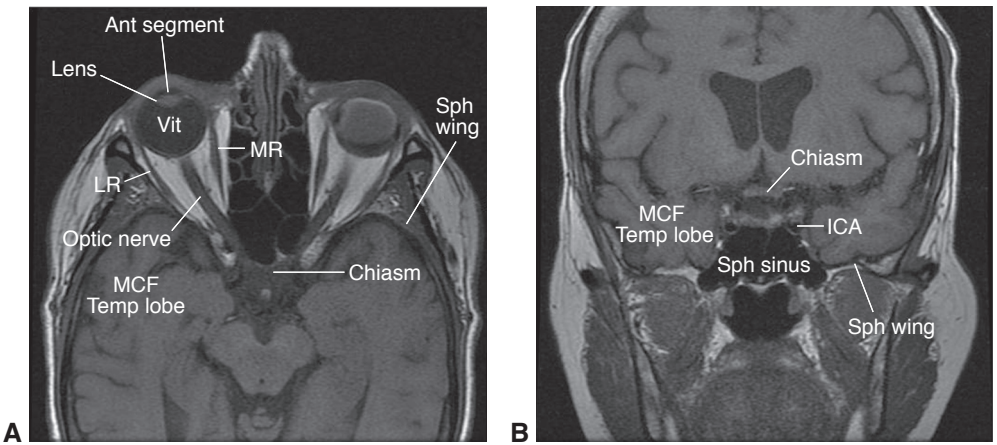


Figure 2-2 Brain and orbital magnetic resonance imaging (MRI) scans showing anatomical visual and orbital structures from the chiasm to the anterior orbit. (The abnormality of the left globe is not pertinent to the objective of this figure.) T1-weighted axial (A), T1-weighted coronal (B–D), T2-weighted coronal with fat saturation (E), and T1-weighted coronal (F) images.

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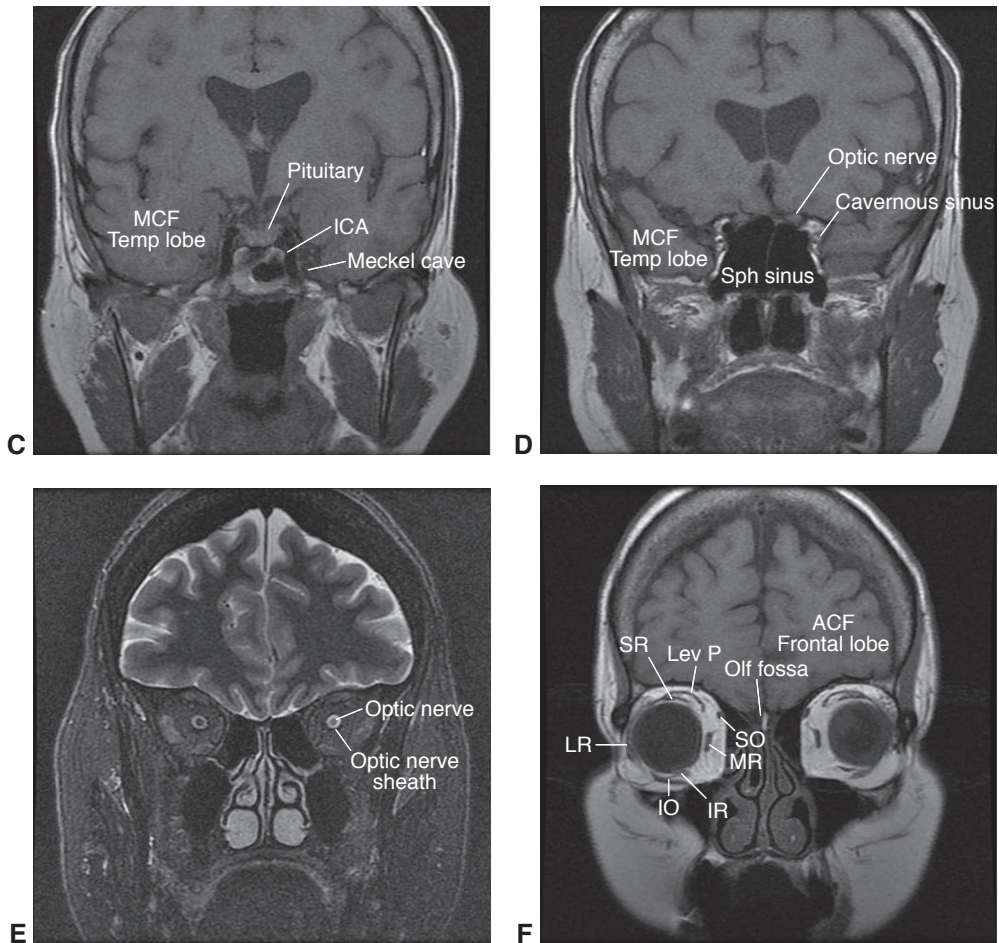


Figure 2-2 (continued) ACF = anterior cranial fossa; Ant segment = anterior segment; ICA = internal carotid artery; IO = inferior oblique muscle; IR = inferior rectus muscle; LR = lateral rectus muscle; Lev P = levator palpebrae superioris muscle; MCF = middle cranial fossa; MR = medial rectus muscle; Olf fossa = olfactory fossa; SO = superior oblique muscle; Sph sinus = sphenoid sinus; Sph wing = sphenoid wing; SR = superior rectus muscle; Temp lobe = temporal lobe; Vit = vitreous. (Courtesy of M. Tariq Bhatti, MD.)

The use of plain (x-ray) film in the evaluation of neuro-ophthalmic diseases has largely become obsolete, except to evaluate for a metallic foreign body. A glossary of select neuroimaging terminology appears at the end of this chapter.

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Lee AG, Johnson MC, Policeni BA, Smoker WR. Imaging for neuro-ophthalmic and orbital disease—a review. *Clin Exp Ophthalmol*. 2009;37(1):30–53.

Computed Tomography

The orbit is particularly well suited to x-ray–based CT imaging because fat provides excellent contrast to the globe, lacrimal gland, optic nerve, and extraocular muscles. Bone and lesions that contain calcium can be easily visualized because of their marked x-ray attenuation. Soft-tissue details can be further enhanced with the injection of iodinated contrast material; this material crosses a disrupted blood–brain barrier and accumulates within a local lesion, revealing inflammatory and neoplastic processes. Iodinated contrast material can be used in patients with a calculated glomerular filtration rate (GFR) greater than 60 mL/min/1.73 m².

Most modern CT scanners image the patient with simultaneous sectioning (ie, spiral or helical) and have multiplanar reconstruction capabilities through the use of a volume-rendering method known as maximum intensity projection (MIP). The advantages of CT include its relatively low cost, rapid image acquisition, wide availability, and excellent spatial resolution. Its speed and ability to accurately identify acute blood or bone abnormalities make CT especially useful when examining trauma patients who may be confused or combative. However, CT scans carry the risk of ionizing radiation. Most national recommendations for dosages are below 150 milliGray (mGy) per scan. The advantages and disadvantages of CT are summarized in Table 2-1.

Magnetic Resonance Imaging

As mentioned, MRI is the imaging method of choice for most patients with neuro-ophthalmic conditions. This technique relies on the magnetic properties of the spinning protons in soft tissue used for image generation. The magnetic field strength is measured in tesla (T); most commercially available machines range from 1–3 T in strength. Open MRI machines are of lower strength and provide poorer image quality. The superior image quality and shorter acquisition times provided by higher-strength machines are based on higher-quality signal-to-noise and contrast-to-noise ratios.

MRI is sensitive to changes in the water content of soft tissue, which depends on how the water is bound and how it moves within the tissue. The patient can be injected with gadolinium, a paramagnetic contrast agent with unpaired electrons in the outer shell; the gadolinium traverses a disrupted blood–brain barrier and alters the MRI signal characteristics. This alteration may be crucial in identifying infectious and inflammatory lesions as well as certain tumors with compositions that make them otherwise indistinguishable from normal cortical tissue. Gadolinium-based contrast agents may cause nephrogenic systemic fibrosis (NSF), a rare, multisystemic disease of the heart, lung, and liver characterized by soft-tissue collagen deposition that results in skin thickening and muscle contractures. Gadolinium-based contrast agents are a relative contraindication in patients with preexisting renal disease and patients who have recently had kidney or liver transplants. Most radiologists will not administer the contrast media if the calculated GFR is lower than 60 mL/min/1.73 m². The advantages and disadvantages of MRI are summarized in Table 2-1.

Table 2-1 Comparison of Magnetic Resonance Imaging and Computed Tomography

	Advantages	Disadvantages	Contraindications
MRI	Better able to distinguish white from gray matter Better able to visualize posterior fossa pathology Better for soft tissue Better resolution of optic nerve and orbital apex Can establish evolution of intraparenchymal hemorrhage No ionizing radiation	Contrast dye reactions and systemic nephrogenic fibrosis Greater cost Susceptibility artifacts from metal (eg, braces) or air–tissue interfaces Longer acquisition time	Cochlear implants Ferromagnetic implants/foreign bodies Gadolinium should not be administered in patients who are pregnant Metallic cardiac valves Non–MRI-compatible intracranial aneurysm clips Pacemakers Renal insufficiency Technical considerations: claustrophobia/too large for the bore
CT	Assessment of bony abnormalities Assessment of orbital and hyperacute intracranial hemorrhage Detection of calcification in lesions Evaluation of globe and orbital trauma (include high-resolution bone algorithms)	Exposure to ionizing radiation dose (CT head radiation dose = 1.5 mGy) Iodine-based dye contrast reactions Lack of direct sagittal imaging Limited resolution in the posterior fossa Poor resolution of the orbital apex	Renal insufficiency: Contraindicated if calculated GFR is lower than 60 mL/min/1.73 m ²
MRA/MRV	Less invasive than catheter angiography	Limited resolution (in aneurysms ≤ 3 mm) May overestimate carotid stenosis or venous sinus stenosis	Same as for MRI
CTA/CTV	Less invasive than catheter angiography	Artifacts from superimposed bone and adjacent vessels, especially where aneurysms lie within or close to bone Limited resolution (in aneurysms ≤ 3 mm)	Same as for CT

CT = computed tomography; CTA = computed tomography angiography; CTV = computed tomography venography; GFR = glomerular filtration rate; mGy = milligray; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; MRV = magnetic resonance venography.

Magnetic resonance images are usually classified as T1- or T2-weighted (Fig 2-3). Each tissue type has a characteristic T1 and T2 relaxation time attributable to the amount of water in the tissue and how the water is bound in the tissue (Table 2-2). In the most common MRI sequence technique, known as *spin echo* (SE), a T1-weighted image is obtained by selecting the appropriate radiofrequency (RF) pulse timing, which is a relatively short time to repetition (TR; approximately 200–700 ms) and a short time to echo (TE; 20–35 ms). The information regarding TR and TE is traditionally displayed on the scan (the position of this information on the display varies according to the image software used). T1-weighted images are optimal for demonstrating anatomy. T1-weighted images also have a higher resolution than T2-weighted images, chiefly because of the increased intensity of the signal and shorter repetition time, which result in faster acquisition times and thereby minimize movement-related artifacts. However, T2-weighted images (long TR of 1500–3000 ms and TE of 75–250 ms) maximize differences in tissue water content and state and thus are more sensitive to inflammatory, ischemic, or neoplastic alterations in tissue (Figs 2-4, 2-5, 2-6). Proton density-weighted images are similar to T2-weighted images but have a long TR and a short TE, both of which allow a clear depiction of white versus gray matter; however, proton density-weighted images have now been replaced by *fluid-attenuated inversion recovery* (FLAIR) images.

Very intense tissue signals (eg, those from fat in T1-weighted images and those from cerebrospinal fluid [CSF] or vitreous in T2-weighted images) may obscure subtle signal abnormalities in neighboring tissues (Table 2-3). Special RF pulse sequences are used to reduce such intense signals. Fat-suppression techniques, such as *short tau inversion recovery* (STIR), are used to obtain T1-weighted images without the confounding bright

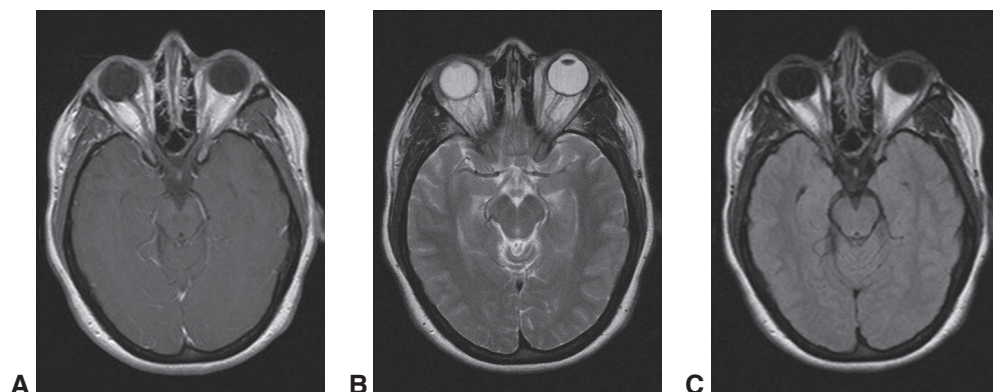


Figure 2-3 Normal axial MRI scans of the brain at the level of the orbits and midbrain, highlighting the different signal characteristics depending on the water content and bound state of the tissue. **A**, T1-weighted image with contrast shows cerebrospinal fluid (CSF) and vitreous as hypointense (*dark*), orbital fat as hyperintense (*bright*), and gray matter as relatively hypointense in comparison to white matter. **B**, T2-weighted image shows that CSF, vitreous, and orbital fat are hyperintense and gray matter is hyperintense in comparison to white matter. **C**, Fluid-attenuated inversion recovery image (FLAIR) shows that orbital fat is hyperintense; however, vitreous and CSF appear hypointense, facilitating detection of abnormalities in periventricular tissue. Note that in the FLAIR image the gray matter is lighter than in the T1-weighted image. (Courtesy of Rod Foroozan, MD.)

Table 2-2 MRI Signal Intensity (Brightness) by Tissue Type

T1	Fat > white matter > gray matter > CSF/vitreous > air
T2/PD	CSF/vitreous > gray matter > white matter > fat
FLAIR	Fat > gray matter > white matter > CSF/vitreous > air
STIR	CSF/vitreous = gray matter > white matter > fat > air

CSF = cerebrospinal fluid; FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; PD = proton density; STIR = short tau inversion recovery.

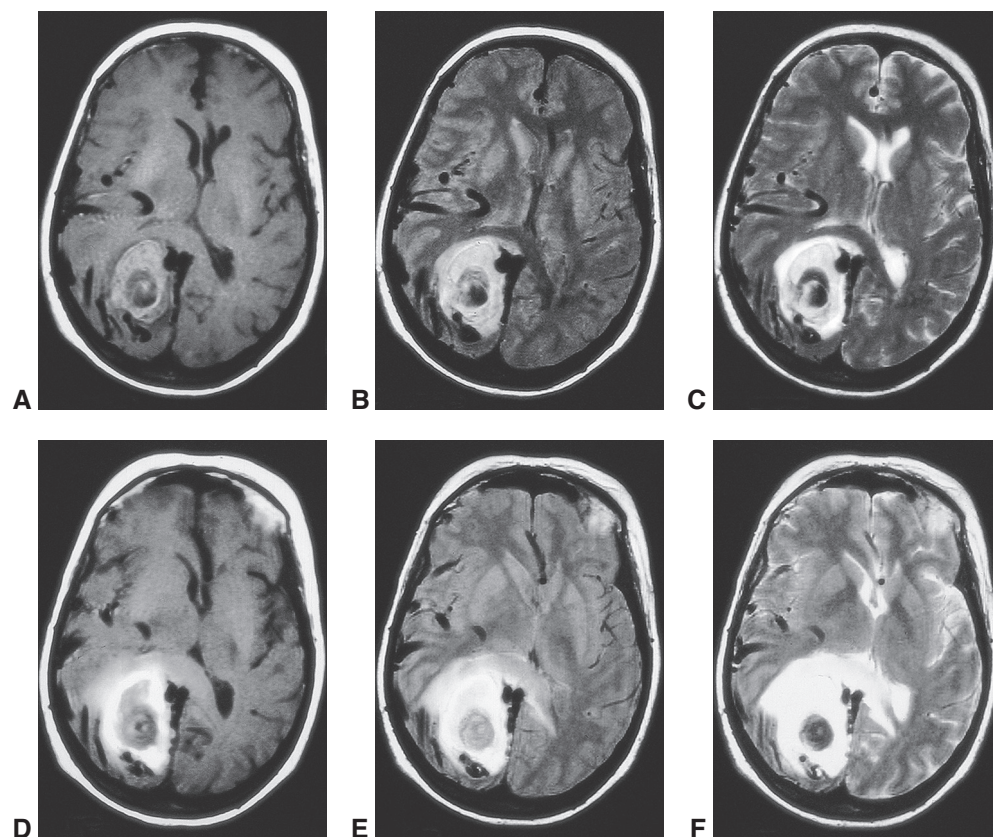


Figure 2-4 A comparison between T1-weighted and T2-weighted MRI scans can yield information about the characteristics of a lesion and can be particularly helpful in dating hemorrhages. A 61-year-old patient presented with acute onset of severe headache. A hemorrhage is apparent in the parieto-occipital region in the 3 original scans: T1-weighted (**A**), proton density (**B**), and T2-weighted (**C**) images. The signal at the lesion periphery relates to the presence of oxyhemoglobin, whereas the core remains dark in all 3 images because of the presence of deoxyhemoglobin. When the MRI series was repeated 10 days later, the signal characteristics had changed as a result of the development of methemoglobin in the outer ring, which is bright on T1-weighted (**D**), proton density (**E**), and T2-weighted (**F**) images. The core remains dark. (Courtesy of Steven A. Newman, MD.)

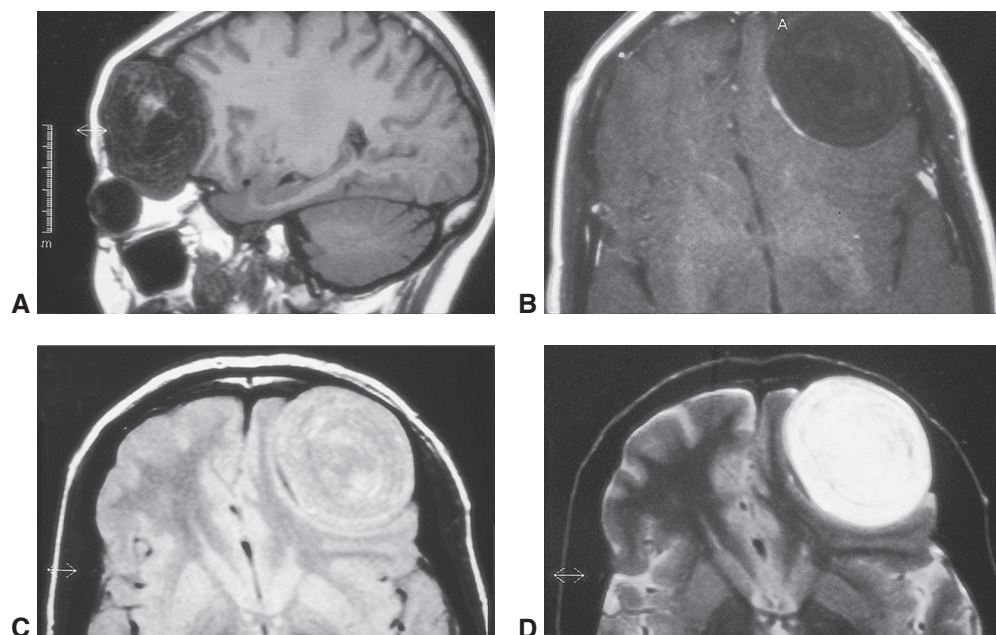


Figure 2-5 Various tumors may have specific sequence findings. This patient had a large frontal tumor invading the orbit. **A**, A T1-weighted sagittal sequence shows the tumor to be heterogeneous but mostly hypointense to gray matter. **B**, A gadolinium-enhanced, T1-weighted axial image demonstrates minimal rim enhancement. **C**, On a proton density image, the signal intensity becomes brighter; it is isointense with gray matter and brighter than white matter. **D**, On a T2-weighted image, the lesion becomes extremely bright. These findings are characteristic of an epidermoid. (Courtesy of Steven A. Newman, MD.)

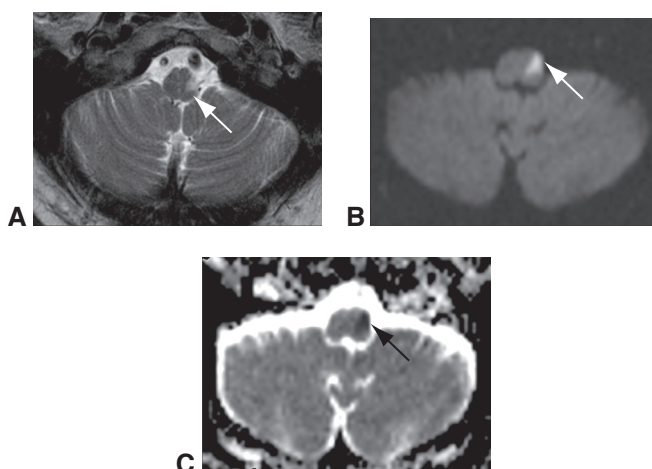


Figure 2-6 MRI scans of a patient with lateral medullary syndrome (also called Wallenberg syndrome). **A**, A T2-weighted axial MRI scan demonstrates a bright signal in the left lateral medulla (arrow). **B**, Diffusion-weighted imaging (DWI) shows a bright signal (arrow). **C**, The apparent diffusion coefficient (ADC) shows a dark signal (arrow) consistent with an acute infarction and not the phenomenon known as T2 shine-through. (Courtesy of M. Tariq Bhatti, MD.)

fat signal. This technique is particularly useful in studying the orbit (Figs 2-7, 2-8; see Fig 2-9D). FLAIR provides T2-weighted images without the high (bright)-CSF signal, making this imaging modality ideal for detecting periventricular white matter changes in a demyelinating process such as multiple sclerosis (Fig 2-9).

Table 2-3 Edema: DWI and ADC

Type of Edema	DWI Signal	ADC Signal
Cytotoxic	Bright (high or restricted diffusion)*	Dark (low)
Vasogenic	Dark (low)	Normal (sometimes bright)

ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging.

*Bright signal on DWI represents restricted diffusion or decreased water movement.

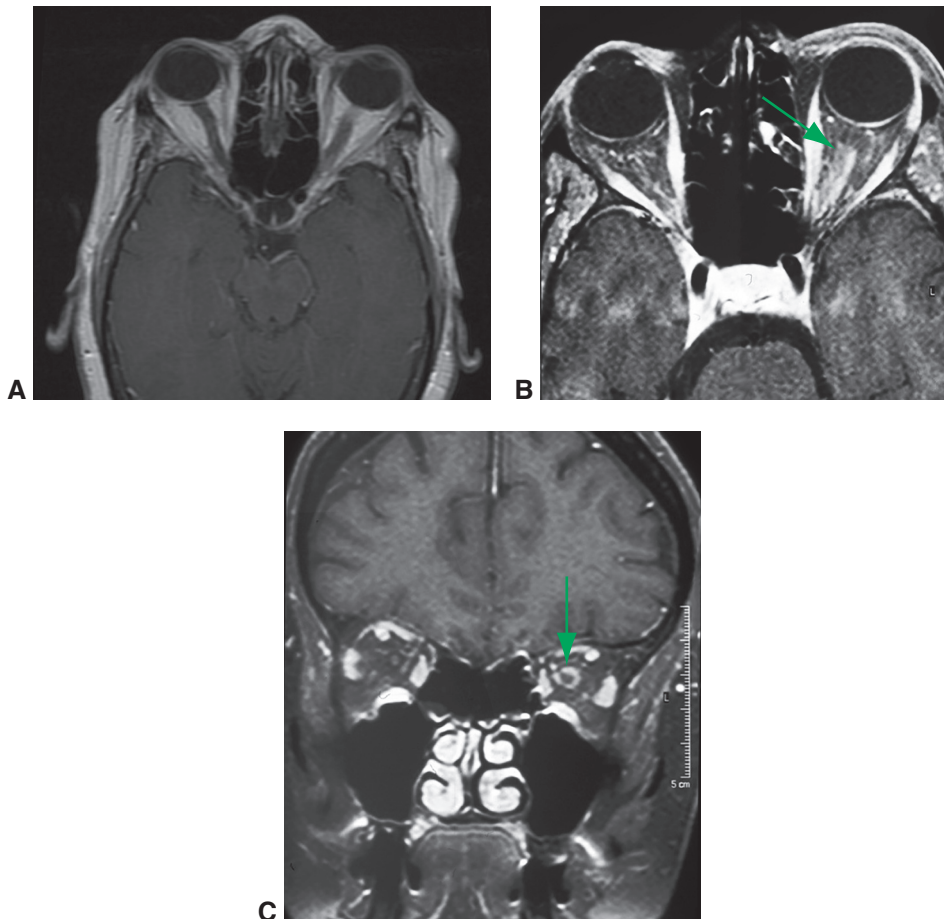
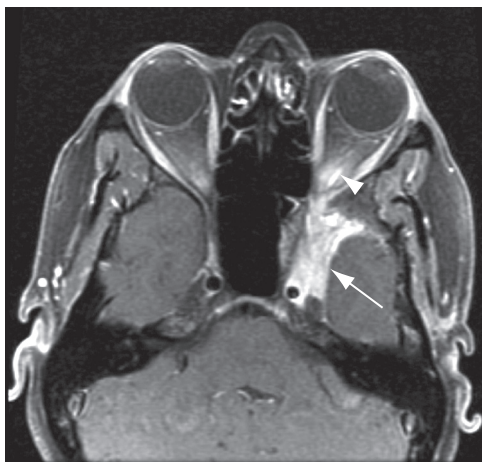


Figure 2-7 MRI scan of a patient with left optic nerve sheath meningioma. **A**, A T1-weighted axial orbital MRI scan shows the normal hyperintense orbital fat. **B**, Suppression of the orbital fat allows visualization of the optic nerve sheath enhancement (*arrow*) consistent with a meningioma. **C**, A T1-weighted coronal postcontrast image with orbital fat suppression shows enhancement of the optic nerve sheath (*arrow*). (Courtesy of Valerie Biousse, MD.)

Figure 2-8 MRI scan from a 48-year-old woman who presented with slowly progressive decreased vision in the left eye. The T1-weighted axial postcontrast image with fat suppression shows a meningioma involving the middle cranial fossa of the skull base (*arrow*), including the optic canal. Abnormal enhancement in the orbital apex indicates that the meningioma extends along the optic nerve sheath (*arrowhead*). (Courtesy of Eric Egenberger, DO.)



Diffusion-weighted imaging (DWI) is sensitive to recent alterations in vascular perfusion and is thus ideal for identifying recent infarctions (Fig 2-10; see also Fig 2-6). An abnormal DWI signal occurs within minutes of the onset of cerebral ischemia (versus several hours with conventional MRI sequences) and persists for approximately 3 weeks, thus serving as a time marker for acute and subacute ischemic events. *Apparent diffusion coefficient (ADC)* is a derived image technique used for stroke and oncological imaging. ADC can help determine whether the DWI hyperintensity is real diffusion restriction or a T2 “shine-through” artifact (see Table 2-3).

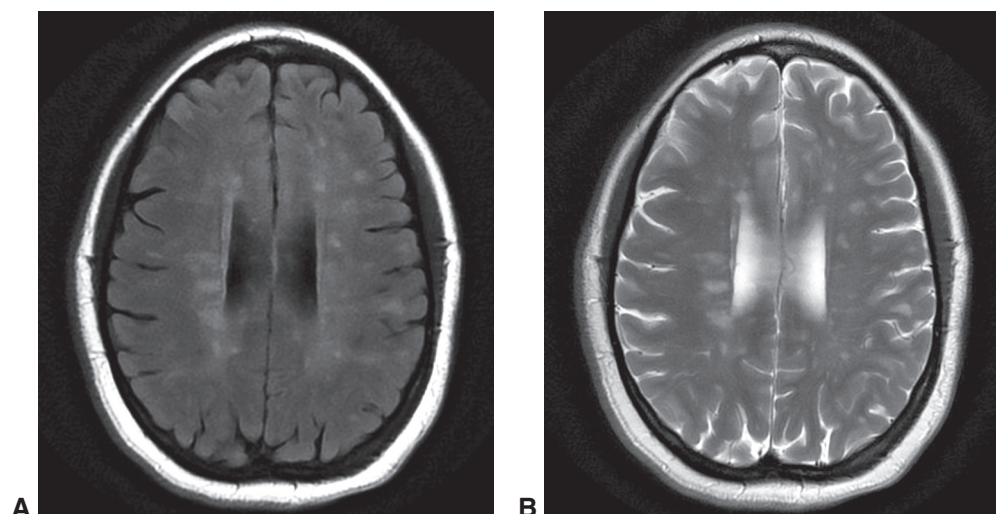


Figure 2-9 MRI scans of a 30-year-old woman with acute optic neuritis of the left eye. An axial FLAIR image (**A**) and an axial T2-weighted image (**B**) show bilateral, scattered, periventricular white-matter hyperintense lesions, which are more conspicuous on the FLAIR image.

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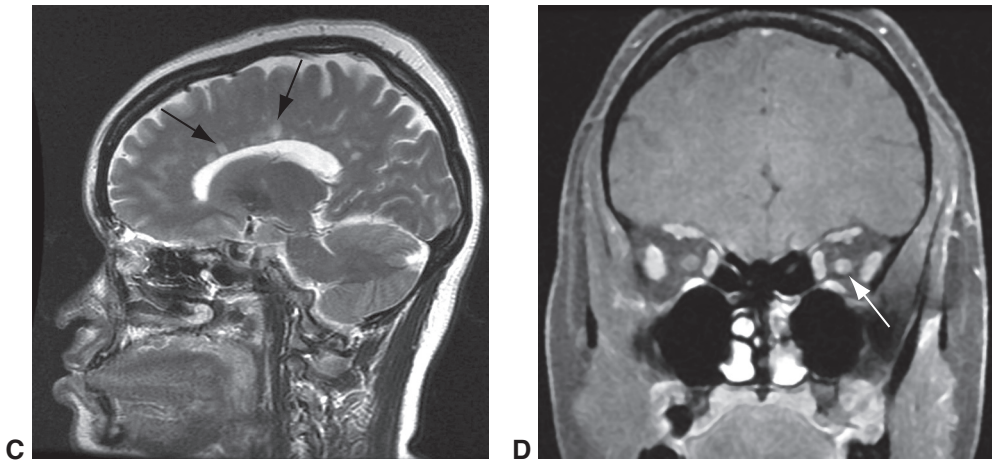


Figure 2-9 (continued) **C**, AT2-weighted sagittal image demonstrates the same periventricular white matter changes perpendicular to the corpus callosum (*arrows*), also known as Dawson fingers. **D**, A T1-weighted coronal postcontrast image with orbital fat suppression shows enhancement of the left optic nerve (*arrow*). (Courtesy of M. Tariq Bhatti, MD.)

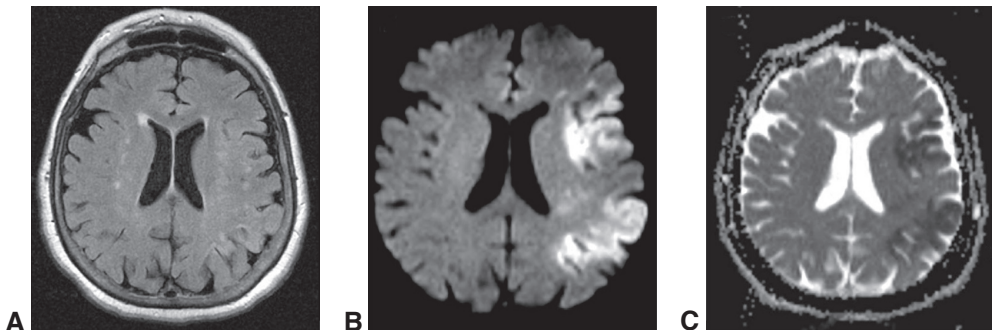


Figure 2-10 Axial MRI scans demonstrate the value of DWI in acute infarction. **A**, The FLAIR image is normal except for nonspecific tiny foci of hyperintense signal in the deep white matter. **B**, DWI reveals abnormal restricted diffusion (high-intensity signal) near the left middle cerebral artery. **C**, The low-intensity signal on the ADC map is consistent with an acute infarction. (Courtesy of M. Tariq Bhatti, MD.)

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Vascular Imaging

Several techniques are commonly used to image blood vessels; obtaining these images is important because of the frequency with which ischemic processes affect the nervous system.

Catheter Angiography

The gold standard for intracerebral vascular imaging remains catheter angiography (Fig 2-11). With this technique, a catheter is placed intra-arterially and iodinated radiodense contrast dye is injected. *Digital subtraction angiography (DSA)* is a technique that reduces artifacts by subtracting densities created by the overlying bony skull. The contrast dye outlines the column of flowing blood within the injected vessel and demonstrates stenosis, aneurysms, vascular malformations, flow dynamics, and vessel wall irregularities such as dissections or vasculitis. The procedure has an overall morbidity of approximately 2.5%, primarily related to ischemia from emboli or vasospasm, dye-related reactions, or complications at the arterial puncture site (eg, hematoma). The use of digital subtraction technology has enhanced the ability to visualize vascular structures with smaller amounts of contrast dye.

Magnetic Resonance Angiography and Magnetic Resonance Venography

Because an MRI signal requires detection of a brief period of excitation and decay, moving tissue often passes out of the plane of assessment before the return signal can be detected, resulting in the black “flow void” that characterizes MRI scans of vascular channels with flow. However, protons that are excited in one slice and then move to another may be specifically imaged using the 3-dimensional assessment technique that underlies MRA and MRV. MRA signals may also be obtained from gadolinium-enhanced images. This technique is particularly useful for imaging the proximal large vessels of the chest and neck. MRA with gadolinium contrast has a very short acquisition time, reducing the potential for patient movement–related artifacts. MRA provides excellent noninvasive information about large- and medium-size vessels (Fig 2-12). Because MRA depends on flow physiology, it tends to overestimate vascular stenosis, and the reduced image resolution limits the

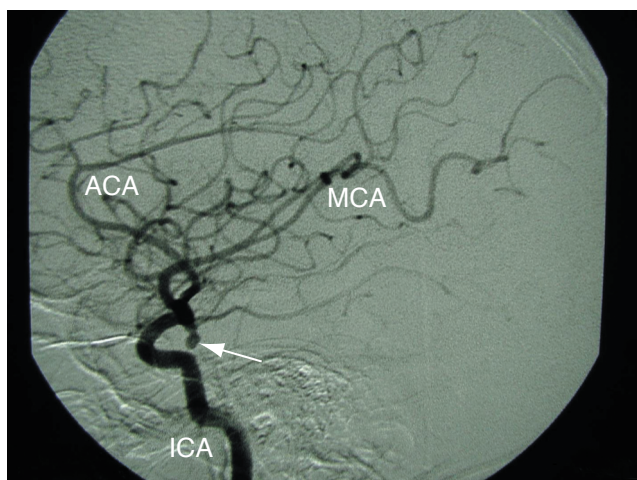


Figure 2-11 A contrast angiogram, lateral view, demonstrates an aneurysm of the posterior communicating artery (arrow). ACA = anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery. (Courtesy of Rod Foroozan, MD.)

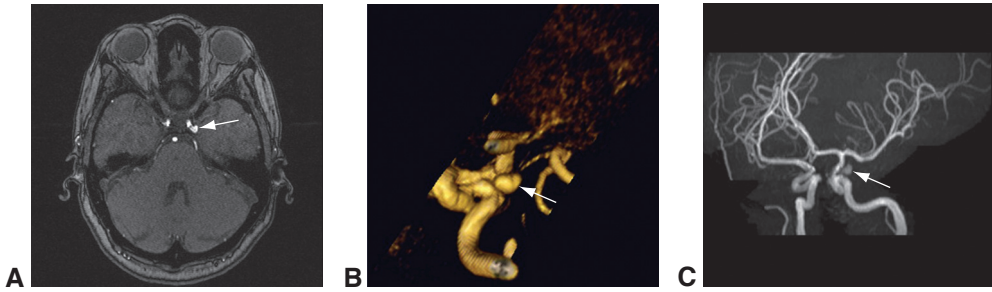


Figure 2-12 Magnetic resonance angiography (MRA) provides excellent noninvasive information about large- and medium-size vessels. **A**, An MRA source image shows an abnormality at the junction of the posterior communicating artery and internal carotid artery (*arrow*). A volume-rendered 3-dimensional image (**B**) and a maximal intensity projection image (**C**) clearly show a posterior communicating artery aneurysm (*arrows*). (Courtesy of M. Tariq Bhatti, MD.)

ability to visualize smaller vessels or vasculitis. MRV may be helpful in excluding thrombosis within the dural venous sinuses (Fig 2-13), a condition that may cause papilledema (see Chapter 14).

Computed Tomography Angiography and Computed Tomography Venography

CTA uses a high-speed spiral scanner that provides excellent vessel resolution, with 3-dimensional capability that is complementary to that of MRA. The technique requires use of iodinated contrast dye, employs ionizing radiation, and takes approximately 15 minutes to complete. Sensitivities in the detection of aneurysms wider than 3 mm

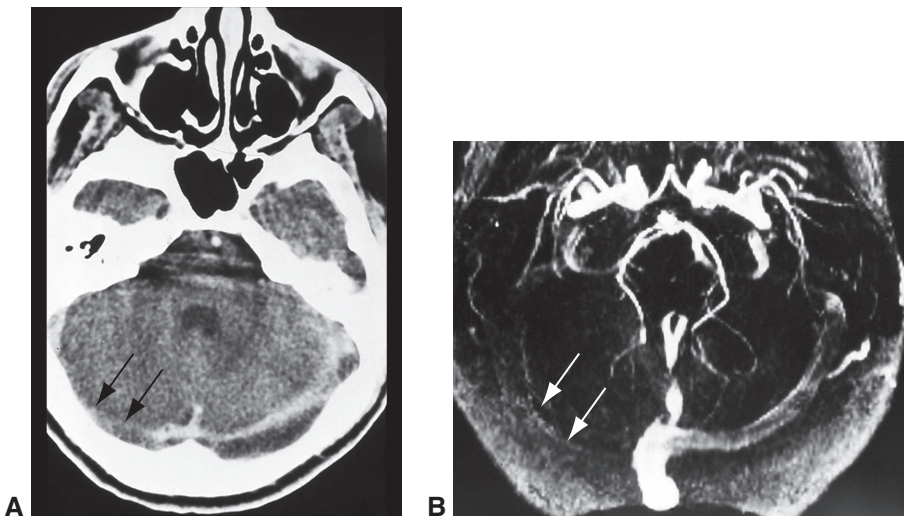


Figure 2-13 Venous sinus thrombosis. **A**, Postcontrast axial CT scan shows a right-sided transverse sinus thrombosis (*arrows*). **B**, The magnetic resonance venography scan with contrast shows a complete thrombotic occlusion of the right transverse sinus (*arrows*). (Courtesy of Paul H. Phillips, MD.)

in diameter or stenosis greater than 70% are approximately 95%. Some medical centers prefer the use of CTA to MRA for the detection of cerebral aneurysms, including those causing an ocular motor cranial nerve (CN) palsy (see Chapter 7, Fig 7-9). New multi-detector CTA techniques can accurately detect aneurysms greater than 3–4 mm in diameter in nearly all patients with CN III palsies. CTV is an excellent imaging modality for visualizing the cerebral venous system and is less susceptible to artifacts in comparison to MRV.

Mathew MR, Teasdale E, McFadzean RM. Multidetector computed tomographic angiography in isolated third nerve palsy. *Ophthalmology*. 2008;115(8):1411–1415.

von Kummer R, Dzialowski I, Gerber J. Therapeutic efficacy of brain imaging in acute ischemic stroke patients. *J Neuroradiol*. 2015;42(1):47–54.

Metabolic and Functional Imaging Modalities

Magnetic resonance spectroscopy (MRS) is used for diagnostic in vivo biochemistry and can provide information about the integrity and metabolism of neural tissue. MRS can help distinguish edema from a tumor. *Functional MRI (fMRI)* depends on changes in regional blood flow in the brain in response to performing specific cognitive, sensory, or motor tasks. The biochemical basis of most fMRI techniques is the measurement of differences in blood oxygenation level–dependent (BOLD) responses during performance of these specific tasks. fMRI is useful for intraoperative monitoring and in the evaluation of patients with cortical vision loss. *Positron emission tomography (PET)* is performed with the systemic administration of a short-half-life radioisotope, such as fluorodeoxyglucose (FDG), followed by imaging of the positrons produced during their decay. PET shows metabolic perfusion and can detect hypometabolism in patients with visual cortical dysfunction. *Single-photon emission computed tomography (SPECT)* uses an iodinated radio-tracer or technetium-99m as a cerebral perfusion and extraction agent. SPECT is more widely available than PET, but it has poorer resolution and specificity. Functional imaging may reveal altered regional cerebral metabolism in patients with cerebral vision impairment from various causes in patients who have a normal MRI.

Ultrasonography

Ultrasonography is a noninvasive, relatively inexpensive, rapid, office-based technique for imaging the globe, orbit, and carotid arteries. The images are based on the reflection of 8–20 MHz (megahertz) ultrasound waves at acoustic interfaces. One form of ultrasonography, *carotid Doppler imaging*, is generally accurate at detecting cervical carotid artery stenosis, but it does not provide information about the more proximal or distal vessels. The primary use of carotid Doppler imaging in neuro-ophthalmology is detection of cervical carotid artery stenosis in patients with transient monocular blindness that is suggestive of retinal or optic nerve ischemia. It is not accurate at detecting carotid artery dissection.

Orbital Doppler sonography is useful in the evaluation of a suspected carotid-cavernous fistula by detecting reversal of normally retrograde venous blood flow within the superior ophthalmic vein. Orbital ultrasound provides data concerning the retrobulbar structures,

including extraocular muscles, optic nerve, and vessels, but it does not provide accurate imaging of the orbital apex. Ultrasound is also useful for evaluating the optic nerve head (ONH) and can help distinguish ONH edema from ONH drusen; the latter is strongly echogenic (see Chapter 4, Fig 4-22).

Crucial Questions in Imaging

Although neuroimaging is widely available, it remains expensive and is not without risks. Accordingly, it is crucial that the clinician addresses the following issues within the context of a specific clinical dilemma when planning the use of an imaging study as part of a neuro-ophthalmic workup (Table 2-4):

- *when* to order
- *what* to order
 - modality
 - location
- *how* to order
 - specify lesion and region of interest
 - discuss with radiologist before ordering
 - review with radiologist after imaging

When to Order

The decision concerning when to order an imaging study should be based on clinical localization and the expectation of particular findings. Furthermore, the information acquired by imaging should have some influence on patient management or provide a more accurate prognosis of the disease's natural history. For those patients with visual symptoms that are believed to herald an emergent neurological or life- or vision-threatening condition, there should be no delay in performing the necessary testing to confirm the diagnosis and immediately commence treatment.

What to Order

With some important exceptions (see Table 2-1), MRI is usually more valuable than CT in detecting a lesion and narrowing the differential diagnosis. The specific choice of imaging modality, including the sequence, orientation, and direction, depends on a combination of the suspected location and the expected pathology. In suspected large-vessel disease, MRA, CTA, and DSA may also be considered.

Imaging of both the brain and the orbits should be performed. Orbital imaging provides details about the optic nerves and the surrounding tissues that often are not detected with brain imaging alone.

When pathology is localized to the orbit, either CT or MRI can provide useful information. Orbital fat provides excellent contrast with the other orbital components on CT and MRI, and both modalities give excellent anatomical localization (see Figs 2-1, 2-2, 2-5).

Table 2-4 Imaging Choice Based on Clinical Scenario

Clinical Scenario	Imaging Study	Comments
Acute hemorrhage	CT, MRI	CT better for acute subarachnoid hemorrhage; MRI clarifies evolution of intraparenchymal hemorrhage
Aneurysm	MRA, CTA, angiography	May be missed by MRI and CT
Arteriovenous malformation	Angiography	
Bone disease	CT	
Calcification	CT	Most forms poorly visualized on MRI
Carotid cavernous fistula	MRA, angiography	MRA prior to angiography
Carotid dissection	MRI, MRA, CTA	
Carotid stenosis	Doppler, MRA, CTA, angiography	
Cerebral vascular disease	MRA, CTA, CTV	
Cerebral venous disease	MRI, MRA, MRV	
Chiasmal syndrome	MRI	Poorly visualized on CT
Demyelination or multiple sclerosis	MRI	FLAIR best for demyelinating lesions; poorly visualized on CT
Foreign body	CT	MRI problematic with ferromagnetic objects, such as vascular clips
Infection	MRI	Abscess, meningitis
Meningeal disorders	MRI	Infectious, inflammatory, or neoplastic process
Middle cranial fossa disease	MRI, CT	
Neoplasm	MRI	MRI better for edema and features, less so for bony involvement
Optic neuritis	MRI	Include contrast and fat suppression; CT poor
Orbitopathy	MRI, CT	Include fat suppression with MRI
Paranasal sinus disease	CT, MRI	CT shows bony details better than MRI
Parasellar disease	MRI	CT: bony artifact
Pituitary adenoma	MRI	CT in axial plane often misses pituitary abnormalities
Posterior cranial fossa disease	MRI	CT: bony artifact
Radiation damage	MRI	Use contrast with MRI; poorly visualized on CT
Thyroid eye disease	MRI, CT, US	MRI should be done with orbital fat-suppression technique
Trauma	CT	Faster; shows acute blood and bony changes
White matter disease	MRI	Poorly visualized on CT

CT = computed tomography; CTA = computed tomography angiography; CTV = computed tomography venography; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; MRV = magnetic resonance venography; US = ultrasonography.

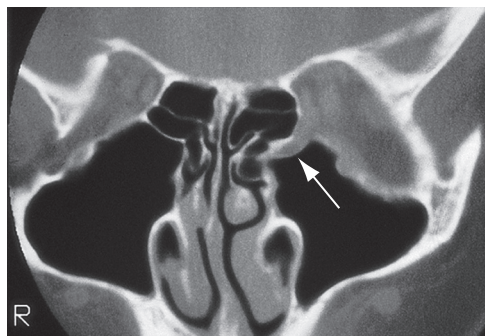


Figure 2-14 A 19-year-old man was referred for evaluation of double vision following a motor vehicle accident. Examination revealed difficulty with adduction of the left eye and a narrowing of the palpebral fissure on attempted abduction of the same eye. Coronal CT scan demonstrates an entrapped left medial rectus muscle (arrow). (Courtesy of Steven A. Newman, MD.)

Direct coronal images are useful in most orbital disorders (Fig 2-14). With MRI, direct coronal imaging is not a problem, but CT may require specific positioning (eg, neck extension) that may be difficult to achieve with elderly patients. MRI of the orbit should be done with fat-saturation techniques designed to eliminate the high-intensity T1 signal from fat (see Figs 2-7, 2-9D).

Luccichenti G, Giugni E, Péran P, et al. 3 Tesla is twice as sensitive as 1.5 Tesla magnetic resonance imaging in the assessment of diffuse axonal injury in traumatic brain injury patients. *Funct Neurol.* 2010;25(2):109–114.

Mafee MF, Rapoport M, Karimi A, Ansari SA, Shah J. Orbital and ocular imaging using 3- and 1.5-T MR imaging systems. *Neuroimaging Clin N Am.* 2005;15(1):1–21.

How to Order

To obtain the most meaningful neuroimaging results, communication with the neuro-radiologist is vital and should include providing a complete patient history, type of scan desired, sequence, contrast material, renal function testing (including the calculated GFR for patients with suspected kidney disease), scan thickness, and area of interest. Failure to supply detailed information often results in images that do not show the area of interest or do so with insufficient detail. Inappropriate images (eg, images showing the wrong location or orientation, lack of contrast administration, or overly thick slices) are often worse than no images at all because they may provide a false sense of security and may create third-party-payer barriers to the required reimaging.

Negative Study Results

When an imaging study fails to demonstrate the expected pathology in relation to the clinical presentation, the clinician's first step is to reexamine the study parameters, ideally with a neuroradiologist. Several questions to keep in mind are:

- Were the appropriate studies performed, including required sequences and orientations?
- Was the area of interest adequately imaged (Fig 2-15)?
- Are the study results truly negative (Fig 2-16)?

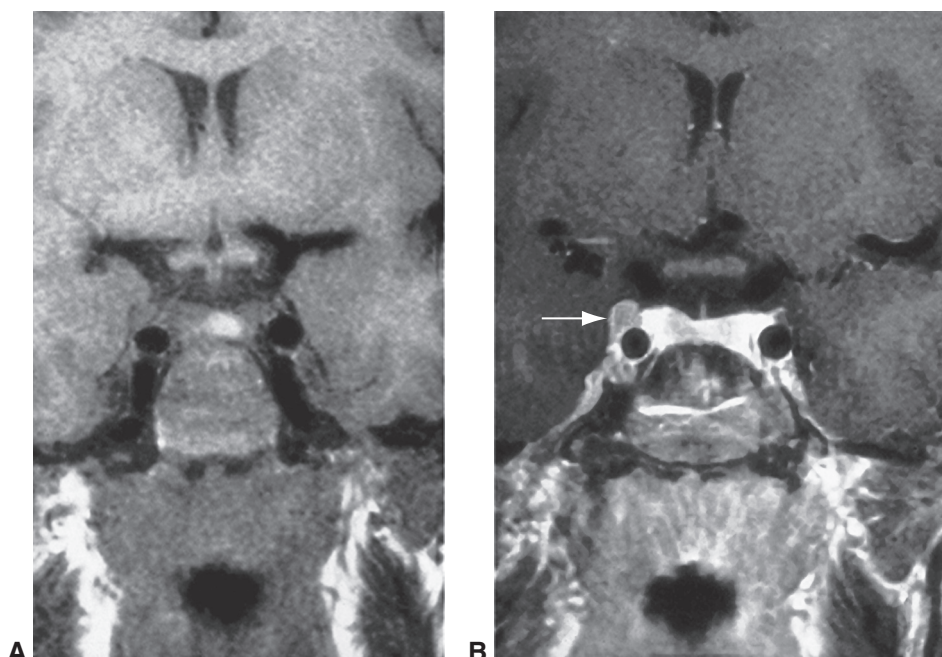


Figure 2-15 Delayed diagnosis of a right cranial nerve (CN) III schwannoma. **A**, Initial MRI results were negative, but fine cuts through the cavernous sinus demonstrated asymmetry, with a slight nodule in the superior portion of the cavernous sinus on the right. **B**, This area became bright following administration of gadolinium contrast, which indicated the presence of a right CN III schwannoma (arrow). (Courtesy of Steven A. Newman, MD.)

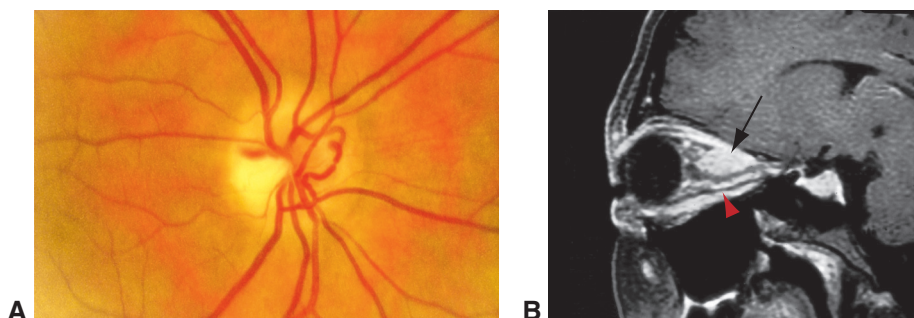


Figure 2-16 A 41-year-old woman was referred for progressive vision loss in the right eye. She had been told she had a swollen optic nerve on the right; her condition was diagnosed as a “mild form of multiple sclerosis.” Her visual acuity was 2/200 OD and 20/20 OS, with a right relative afferent pupillary defect. She had reportedly had 2 previous MRI scans, with negative results. **A**, A fundus photograph of the right optic nerve head demonstrates temporal pallor with opticociliary shunt vessels. The patient was referred for a third MRI scan, but this study was misdirected for workup of “microvascular brainstem disease” and revealed no abnormalities. **B**, A sagittal MRI scan taken through the orbit shows an abnormal optic nerve sheath appearance consistent with an optic nerve sheath meningeoma (arrow). The arrowhead points to the plaque portion of the meningeoma. (Part A courtesy of Steven A. Newman, MD; part B courtesy of Eric Eggenberger, DO.)

Even if the ophthalmologist cannot personally review the studies, speaking directly with the radiologist may prevent certain lesions from being overlooked and can provide the clinical information required to enhance the radiographic report's accuracy and usefulness.

Glossary of Select Neuroimaging Terminology

BOLD (blood oxygenation level–dependent) fMRI technique to demarcate areas of high activity in a patient's brain while the patient performs a specific task.

CTV (computed tomography venography) CT technique in which the venous vasculature is visualized. It is less susceptible to artifacts in comparison to MRV.

DWI (diffusion-weighted imaging) and ADC (apparent diffusion coefficient) MRI techniques used to detect acute and subacute stroke and to differentiate vasogenic from cytotoxic edema.

FLAIR (fluid-attenuated inversion recovery) MRI technique that highlights T2-hyperintense abnormalities adjacent to CSF-containing spaces, such as the ventricles, by suppressing CSF signal intensity.

fMRI (functional magnetic resonance imaging) MRI technique that allows visualization of more active brain areas during a specific task, such as reading.

Gadolinium Paramagnetic contrast agent administered intravenously to enhance lesions.

IR (inversion recovery) and TI (interpulse time) MRI pulse sequence that nulls the bright signal of fat or water to create a FLAIR or STIR image. During MRI, initial 180° radiofrequency pulses are followed by a 90° pulse and immediate acquisition of the signal; in IR sequences, the interpulse time is given by TI.

mGy (milligray) Unit used to measure the absorbed dose of radiation. 1 mGy = 10⁻³ Gy.

MRV (magnetic resonance venography) A MRI imaging technique used to visualize the venous vasculature.

Relaxation Process by which an element releases (re-emits) energy that has been absorbed from the radiofrequency pulses during an MRI sequence.

SE (spin echo) In the most commonly employed SE sequence, a 180° pulse follows a 90° pulse. For T2-weighted images, the 90° pulse is followed by 2 180° pulses. The first 180° pulse is administered at one-half the TE (time to echo), and the second 180° pulse is administered one full TE later. The “first echo” image is referred to as *proton density*, and the “second echo” is T2-weighted.

STIR (short tau [or TI] inversion recovery) MRI technique that suppresses the bright signal of fat by combining short TI inversion recovery and a fast SE sequence.

T1 Time required for 63% of protons to return to the longitudinal plane after cessation of a 90° radiofrequency pulse. This is also referred to as the *longitudinal*, or *spin-lattice*, relaxation time.

T2 Time required for 63% of the magnetic field in the transverse plane created by the radiofrequency pulse to dissipate. This dispersion of the magnetic vector corresponds to the exchange of spin among protons and is referred to as *spin-spin relaxation*; it is completed much more rapidly than is T1 relaxation.

TE (time to echo) Time following the radiofrequency pulse in which the signal is assessed.

Tesla The unit of measure of magnetic field strength.

TR (time to repetition) Time following the radiofrequency pulse to repetition of the pulse.

CHAPTER 3

The Patient With Decreased Vision: Evaluation



This chapter includes a related video, which can be accessed by scanning the QR code provided in the text or going to www.aao.org/bcscvideo_section05.

History

In cases of decreased vision, 3 aspects of the patient's history—in addition to the age of the patient—are crucial in determining the etiology:

1. laterality of the vision loss
2. time course of the vision loss
3. symptoms associated with the vision loss

Unilateral Versus Bilateral Involvement

Establishing the laterality of the vision loss is essential to localization of the lesion. Unilateral vision loss typically indicates a lesion anterior to the chiasm, whereas bilateral vision loss may reflect a bilateral ocular, chiasmal, or retrochiasmal lesion or a systemic process. Patients reporting vision loss should be asked whether they have checked each eye individually. A patient with a right homonymous hemianopia may mistake the temporal visual field defect as a problem with the vision of the right eye only. Binocular involvement might not be appreciated until the patient is examined.

Time Course of Vision Loss

Determining the speed of onset of vision loss can aid the clinician in determining the etiology of the problem. Sudden onset (ie, within minutes) usually indicates an ischemic event, such as arterial occlusion. A course that evolves over days to weeks more typically denotes inflammation. Gradual progression over months or years is typical of compressive lesions, toxic or nutritional optic neuropathies (although such lesions may present more acutely), and glaucoma. It is important to differentiate between sudden loss of vision and sudden awareness of vision loss. Patients may become acutely aware of a chronic processes only upon covering the uninvolved eye or only after the second eye becomes

affected. Although the time course may suggest a cause of vision loss, the time courses of the various etiologies overlap considerably.

Associated Symptoms

Ipsilateral periorbital pain that increases with eye movement occurs commonly in optic neuritis. Associated neurologic symptoms may suggest demyelinating disease. Nonspecific pain, facial numbness, or diplopia may indicate an orbital or cavernous sinus lesion. Headache, jaw claudication, and systemic symptoms suggest giant cell arteritis (GCA).

Examination

Examination of the patient with decreased vision requires performing a full neuro-ophthalmic evaluation.

Visual Acuity Testing

Corrected distance visual acuity (CDVA; also called *best-corrected visual acuity*) should be obtained with refraction. Vision improvement with pinhole viewing indicates a refractive error. For patients with visual acuity levels worse than 20/400, the clinician should quantify CDVA using a standard 20/200 E optotype chart. The clinician records the distance at which the patient is able to discern the letter orientation using standard Snellen notation (eg, “5/200”). This test provides a more accurate and reproducible measurement than does the finger-counting method.

Distance and near corrected visual acuity should be similar; a disparity may suggest a specific pathology. The clinician should document the presence of eccentric fixation (possible central scotoma), tendency to read half of the eye chart (possible hemianopic field defect), or improvement in CDVA when reading single optotypes (which may suggest amblyopia).

Color Vision Testing

Color vision testing complements visual acuity assessment. Optic nerve disease, particularly demyelinating optic neuritis, may disproportionately affect color vision compared with CDVA. In macular disease, visual acuity and color vision tend to decline correspondingly. Thus, an optic neuropathy is the more likely etiology than a maculopathy in the differential diagnosis for an eye with 20/30 visual acuity but with severe loss of color vision. In optic neuropathy, persistent dyschromatopsia can occur even after recovery of visual acuity.

Color vision should be tested separately in each eye to detect unilateral disease. Because Ishihara pseudoisochromatic color plate testing is widely available, it is the commonly used method for color vision evaluation. Although the test was designed to detect congenital red-green color deficiencies, it may also identify acquired dyschromatopsia (though it may miss mild cases). Bilateral, symmetric color vision loss in men may signify congenital dyschromatopsia rather than bilateral optic neuropathies. The Hardy-Rand-Rittler (HRR) plates can be used to screen for tritan (ie, blue-yellow) defects as well as

red-green defects. Blue-yellow color defects often accompany an optic neuropathy but also can occur in a maculopathy.

More detailed color testing may comprehensively characterize a color vision defect. In the Farnsworth panel D-15 test, the patient is asked to arrange 15 colored discs in order of hue and intensity. The Farnsworth-Munsell 100-hue test, which uses 85 colored discs, is the most detailed test and provides the best discrimination. This test requires a substantial amount of time to test and score, thereby limiting its use in routine clinical testing. Color vision testing is discussed further in BCSC Section 12, *Retina and Vitreous*.

Melamud A, Hagstrom S, Traboulsi E. Color vision testing. *Ophthalmic Genet*. 2004;25(3):159–187.

Nichols BE, Thompson HS, Stone EM. Evaluation of a significantly shorter version of the Farnsworth-Munsell 100-hue test in patients with three different optic neuropathies. *J Neuroophthalmol*. 1997;17(1):1–6.

Pupillary Testing

Normally, light directed at 1 pupil causes equal constriction of both pupils (see Chapters 1 and 10). When light is shined into an eye with impaired conduction of the afferent pupillomotor signal along 1 optic nerve, pupillary constriction in both eyes is slower and smaller in amplitude compared with the response that occurs when light is shined into the eye with normal optic nerve conduction. In other words, both the direct and the consensual response are sluggish. This difference between the 2 eyes in pupillary response after light stimulation is known as a relative afferent pupillary defect (RAPD).

The most popular clinical method for detecting an RAPD is the swinging flashlight test (Video 3-1). This test, which compares the pupillary response in the 2 eyes when tested with the same light source, involves swinging a bright light (which is shined directly into the pupil along the visual axis) between the 2 eyes. If the afferent input is significantly asymmetric, the pupils redilate immediately when the light is shined into the affected eye (Fig 3-1).



VIDEO 3-1 Left relative afferent pupillary defect.

Courtesy of M. Tariq Bhatti, MD.

Access all Section 5 videos at www.aao.org/bcscvideo_section05.

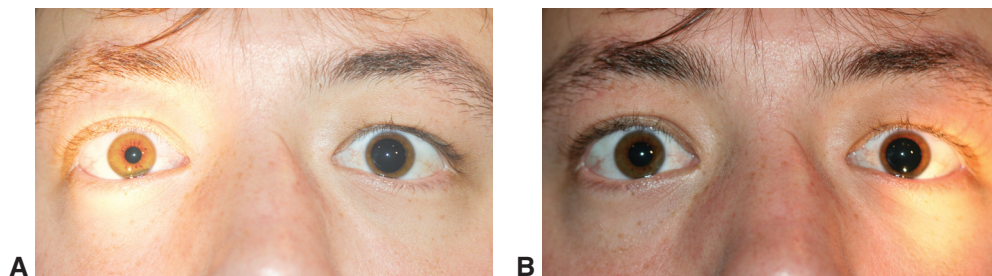


Figure 3-1 Assessing for relative afferent pupillary defect (RAPD) in a patient with left traumatic optic neuropathy; the left pupil is pharmacologically dilated. **A**, The right pupil *constricts* in response to light directed at the right eye only. **B**, The right pupil *dilates* in response to light directed at the left eye only, indicating a left RAPD. (Courtesy of Michael S. Lee, MD.)

TESTING FOR A RELATIVE AFFERENT PUPILLARY DEFECT

1. Dim the ambient lighting; it is easier to evaluate pupillary movement when the pupil size is larger.
2. Ask the patient to fixate at distance to avoid pupillary miosis from accommodation.
3. Use a well-charged, bright, steady source of diffuse light, such as a standard “muscle light.” A light source that is too dim or too bright may produce false-positive or false-negative results, respectively.
4. Stimulate 1 eye for 2–3 seconds, then quickly move across the bridge of the nose to stimulate the other eye for 2–3 seconds. Alternate several times. Do not rely on a single observation.
5. Observe the initial pupillary constriction (velocity and amplitude) and any pupillary dilation. A dense RAPD is easily detected because an affected eye’s pupil dilates when stimulated. A mild-to-moderate RAPD is more difficult to detect because the abnormal pupil may still constrict, but less vigorously than the normal pupil.
6. If 1 pupil does not react (eg, due to iris trauma, synechiae, or pharmacologic mydriasis or miosis), evaluate the direct and consensual responses of the functioning pupil. This may demonstrate the asymmetry of responses and indicate the side of the RAPD (see Fig 3-1).
7. Grade the RAPD 1–4+ in increasing severity or quantify it using neutral-density filters. The filters, placed in front of the unaffected eye, decrease the intensity of the light stimulus. Beginning with the lowest 0.3 log₁₀ unit, repeat the swinging flashlight test. If an RAPD is still detected, place increasingly stronger filters over the unaffected eye until the RAPD “disappears.” At this balance point, the light input from the unaffected eye with the filter matches the light input from the abnormal eye. Quantify the RAPD by the strength of the neutral-density filter needed over the unaffected eye to reach the balance point.

Notes:

Bilateral optic neuropathies, when symmetric, may show sluggish pupillary responses but not a relative difference between the 2 eyes (and therefore no RAPD).

The RAPD magnitude correlates with the degree of damage to retinal ganglion cells and their axons. However, a prominent RAPD can occur with normal visual acuity if significant visual field damage is present.

An RAPD does not cause anisocoria.

An RAPD is an extremely reliable and sensitive indicator of optic nerve dysfunction. Its absence generally indicates either a lack of an optic neuropathy or of bilateral optic nerve involvement. Less commonly, an RAPD may also result from substantial retinal disease, such as a central retinal artery occlusion or retinal detachment. Chiasmal lesions may produce an RAPD secondary to asymmetric optic nerve involvement. In patients with a unilateral optic tract lesion, a mild RAPD may exist on the side of the temporal visual field defect. This has been explained by the difference in light sensitivity between the intact temporal and nasal hemifields. In addition, the proportion of fibers that cross (53%) is greater than the proportion of those that do not cross (47%). In rare cases, an RAPD may result from media opacities such as cataract or vitreous hemorrhage or from amblyopia.

Certain factors, such as dark irides or sluggish, dilated, or miotic pupils, can make it difficult to elicit an RAPD. In these circumstances, subjective sense of brightness and perceived color intensity can be used to identify and quantitatively grade an RAPD. Brightness sense testing requires a bright light source such as a muscle light or an indirect ophthalmoscope set at 6 volts (V). Red perception testing requires a red target, such as the cap of a cycloplegic eyedrop bottle. The clinician directs the patient to look at the target, which is held 30 cm from the eye and is exposed to each eye for the same length of time. The clinician then asks the patient whether the light is of equal brightness (or is equally red) in both eyes. If the patient indicates a difference between the eyes, the target is held in front of the “brighter” or “redder” eye first, before the target is switched to the other eye. The patient is asked, “If the light is 100% bright (the target is 100% red) in this eye, then what percentage is it in the other eye?”

Danesh-Meyer HV, Papchenko TL, Savino PJ, Gamble GD. Brightness sensitivity and color perception as predictors of relative afferent pupillary defect. *Invest Ophthalmol Vis Sci*. 2007;48(8):3616–3621.

Kawasaki A, Miller NR, Kardon R. Pupillographic investigation of the relative afferent pupillary defect associated with a midbrain lesion. *Ophthalmology*. 2010;117(1):175–179.

Fundus Examination

A fundus examination may reveal media opacities or fundus abnormalities that explain a patient's decreased vision. The clarity of the view with the direct ophthalmoscope can suggest how much visual impairment is caused by these media opacities. Using either direct ophthalmoscopy or slit-lamp biomicroscopy, the clinician can assess the appearance of the optic nerve head (ONH) and macula. The ONH is examined for evidence of pallor, edema, excavation, or other abnormalities; the macula is examined for evidence of pigmentary disturbance, edema, scarring, or other disruption of structural integrity.

ONH pallor indicates optic atrophy, which is the hallmark of damage to the retinal ganglion cells. Although the examiner is only able to observe pallor of the neuroretinal rim, ONH pallor can occur from damage to any portion of the ganglion cells, from the ganglion cell bodies to their synapses at the lateral geniculate nucleus. ONH pallor does not occur immediately after injury but takes at least 4–6 weeks from the time of axonal damage. Severe damage causes the ONH to appear chalky white (Fig 3-2). Mild forms of pallor remain more difficult to detect. Evaluation of the capillary net, the network of fine blood vessels on the ONH, may be helpful; the net becomes thin or absent in early atrophy

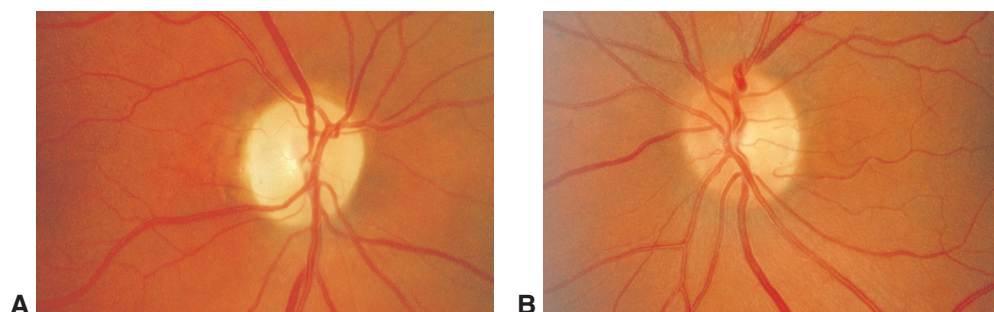


Figure 3-2 Optic nerve head (ONH) pallor. **A**, Diffuse optic atrophy. **B**, Normal ONH appearance. (Courtesy of Steven A. Newman, MD.)

even when pallor is still very mild. In addition, dropout of the retinal nerve fiber layer (RNFL) may precede atrophy. When viewed with a red-free filter, fine defects appear as dark bands among normal striations. These defects, called *rake defects* owing to their similarity to rake marks in soil (Fig 3-3), initially affect the thickest portion of the RNFL, the superior and inferior arcades. However, true temporal pallor must be carefully distinguished from the pallor of the ONH in a pseudophakic eye. If only 1 eye is pseudophakic, the difficulty of comparing ONH pallor in the 2 eyes makes this task particularly challenging.

ONH edema results from impaired axoplasmic flow from any cause, including increased intracranial pressure, local mechanical compression, ischemia, and inflammation. ONH and retinal vascular changes can also accompany ONH edema (Fig 3-4). Regardless of cause, the following clinical features of ONH edema may be observed:

- elevation of the ONH with variable filling in of the physiologic cup; retinal vessels may appear to drape over the elevated ONH margin
- blurring of the ONH margins
- peripapillary RNFL opacification; the RNFL becomes grayish white and opalescent with feathered margins, obscuring portions of the retinal vessels that course within this level of the retina
- hyperemia and dilation of the ONH surface capillary net
- retinal venous dilation and tortuosity
- peripapillary hemorrhages, exudates, or cotton-wool spots
- retinal or choroidal folds or macular edema

Figure 3-3 Rake defects. ONH shows temporal pallor with a broad region of nerve fiber layer dropout (*left*), contrasted with glistening intact nerve fiber layer (*right*). (Courtesy of Anthony C. Arnold, MD.)

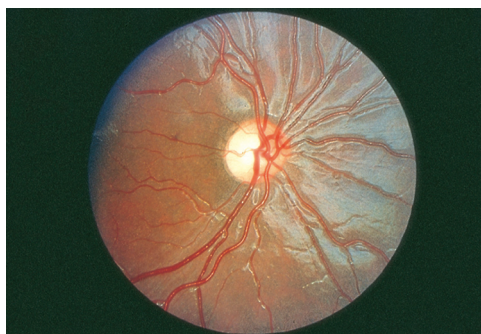




Figure 3-4 Papilledema. **A**, Right eye. **B**, Left eye. The ONH margins are blurred, with grayish-white, opalescent thickening of the peripapillary nerve fiber layer (arrows), cotton-wool spots, and flame hemorrhages. The retinal vessels are partially obscured at the ONH margin and within the peripapillary retina. (Courtesy of Sophia M. Chung, MD.)

Visual Field Evaluation

Evaluation of the visual field helps localize a lesion along the afferent visual pathway, defines patterns of vision loss, and quantifies the defect, enabling measurement of change over time. The choice of technique depends on the degree of detail required and the patient's ability to cooperate. Patterns of visual field loss are discussed in detail in Chapter 4.

Confrontation testing

Confrontation testing, which is easily performed at a patient's bedside or in the clinic, should take place during every ophthalmic examination. It is only a screening test and does not replace formal perimetry. The accuracy of confrontation testing depends on the density of the visual field defect. Accepted methods of confrontation testing include:

- *Description of the examiner's face.* The examiner sits 1 m from the patient. The patient covers 1 eye and fixates on the examiner's nose. The examiner asks the patient whether he or she is unable to see specific parts of the examiner's face. Affirmative responses may aid in identifying central or altitudinal (superior or inferior hemifield) visual field defects.
- *Finger counting in the 4 quadrants.* The patient is asked to count 1 or 2 static fingers as they are presented sequentially in each of the 4 quadrants. The fingers are presented approximately 20° eccentric to fixation and equidistant from the quadrant borders. This technique tests for both altitudinal defects of the anterior visual pathways and homonymous defects due to retrochiasmal lesions.
- *Kinetic red target test.* A 5-mm, red-topped pin is moved inward from beyond the boundary of each quadrant along a line bisecting the horizontal and vertical meridians. The patient is asked to report when the pin is first perceived to be red.
- *Finger or red comparison test.* With the finger comparison test, the examiner's index fingers are presented simultaneously on either side of the vertical meridian, first in the superior and then in the inferior quadrants. The patient is asked to report

whether the fingers are equally in focus. During finger testing, children and non-verbal adults may be asked to mimic the examiner's finger movements. If the patient cannot identify fingers to mimic finger movements, the examiner presents progressively stronger stimuli, such as hand movement or light perception in each quadrant. In the red comparison test, 2 identical red targets are presented in the same manner as the fingers in the finger comparison test. The patient is asked whether the targets are equally red. Color may appear altered, washed out, or absent in a damaged hemifield. Slow movement of the target across the vertical meridian may identify an abnormality in color vision, which suggests damage to the chiasmal or retrochiasmal pathway.

Although these confrontation tests offer high sensitivity, their use is likely to result in many false-positives due to the low specificity of the tests. The single test with the best combination of sensitivity (74%) and specificity (93%) is kinetic testing with a red target.

Extinction refers to the inability to see a target in an affected hemifield *only* during simultaneous stimulation of both hemifields. A target presented only in the affected hemifield can be seen. This finding of visual neglect is characteristic of parietal lobe lesions.

Kerr NM, Chew SS, Eady EK, Gamble GD, Danesh-Meyer HV. Diagnostic accuracy of confrontation visual field tests. *Neurology*. 2010;74(15):1184–1190.

Amsler grid testing

Amsler grid testing screens the central 20° of the visual field (10° from fixation). The patient, with optical correction for near vision as needed, holds the Amsler grid at one-third of a meter, covers 1 eye, and looks at a fixation point in the center of the grid without scanning the grid. The patient describes any areas of distortion (ie, metamorphopsia); such areas suggest macular rather than optic nerve disease. Peripheral “bending” of the grid may represent optical aberration from spectacles and should be disregarded. The patient can also identify any scotoma. Although Amsler grid testing is rapid and simple, its sensitivity is low.

Perimetry

Perimetry provides more detailed evaluation of the visual field. In both static and kinetic techniques, the visual field is analyzed for areas of decreased sensitivity, both in location and in degree. In *static* testing, stimuli turn on and off at designated points within the region of the visual field being tested. In *kinetic* testing, a stimulus moves from a nonseeing to a seeing area of the visual field to determine the location at which it is consistently detected by the patient. All points of equal sensitivity for a specific stimulus are connected to form an isopter, which represents the outer limit of visibility for that stimulus. Analysis of several isopters (plotted with different stimuli) produces a “contour map” of the island of vision.

Kinetic perimetry Kinetic perimetry (eg, Goldmann perimetry, the kinetic program on an Octopus perimeter [Haag-Streit, Köniz, Switzerland]) can be used to evaluate the entire visual field. Stimuli of varying sizes and intensities are moved along each radial meridian from a peripheral to central location. Typically, 2 or 3 isopters are plotted. Varying the stimulus size, intensity, and location can delineate the depths and borders of defects. Kinetic perimetry requires a skilled and knowledgeable perimetrist who can interact with patients to elicit optimal cooperation.

Automated static perimetry Automated static perimetry is considered the gold standard for evaluating visual field defects. Although this method is particularly difficult to use with older or inattentive patients, it possesses numerous advantages over manual kinetic perimetry techniques:

- standardized testing conditions, which improve serial and inter-institutional comparisons of results
- less dependence on technicians
- better sensitivity
- numerical data amenable to statistical analysis for comparisons and clinical studies
- results amenable to electronic data storage

Most automated perimeters use static stimuli that are similar in size to the kinetic perimeter size III stimulus. The perimeter randomly presents stimuli at predetermined locations within a specified region of the visual field. Because nearly 80% of the visual cortex correlates to the central visual field, testing the central 24° or 30° of the visual field is typically adequate for detecting most visual defects (Fig 3-5). It is also critical to measure the foveal threshold (the normal range is 30–37 dB) because it estimates central visual function. Because of the 6° test spacing of the 30-2 and 24-2 programs, 10-2 perimetry may better delineate a small central or paracentral scotoma.

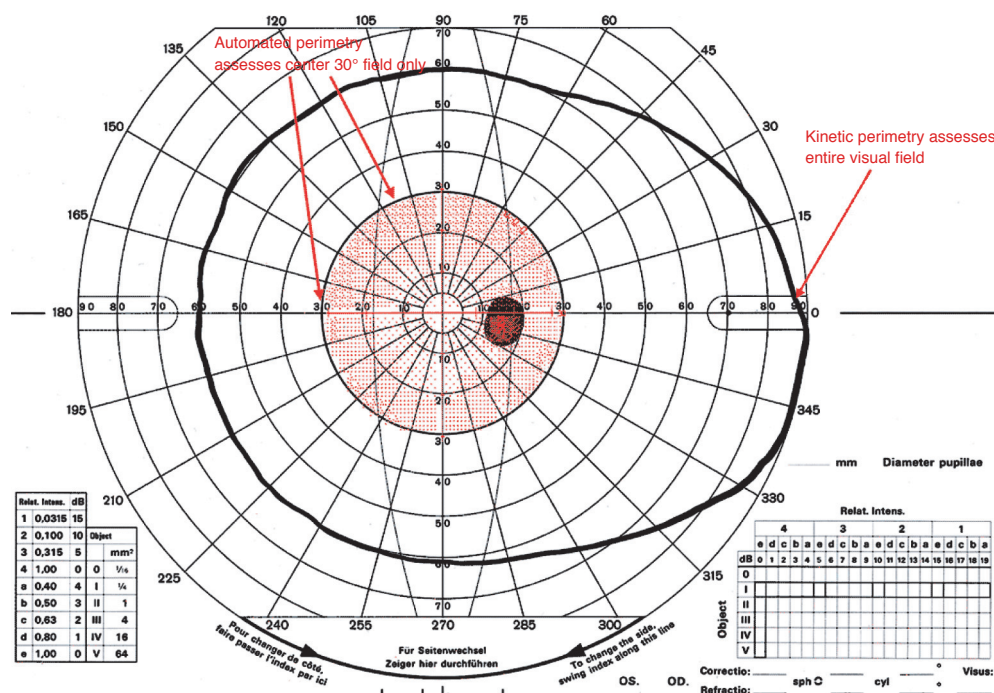


Figure 3-5 Kinetic versus automated perimetry. Diagrammatic representation of the extent of the visual field evaluated by kinetic perimetry versus the 30° central program in automated static perimetry. The largest isopter in kinetic perimetry testing extends 90° temporally and 60° in other quadrants; typical automated static perimetry evaluates only the central 30°. (Courtesy of Anthony C. Arnold, MD.)

The stimuli vary in brightness, and patient responses determine the minimum visible stimulus at each location—the sensitivity threshold. This threshold is defined as the intensity of the dimmest target identified 50% of the time at a given location. For each region tested, the report displays the threshold value in decibels (on a logarithmic scale of intensity, measuring attenuation from the maximum stimulus of the perimeter). For a given stimulus location, a higher value indicates that the patient can see a dimmer stimulus, reflecting greater visual sensitivity at that location. The measured values are not absolute numbers and are not equivalent among perimeters because the machines have different maximum intensities, backgrounds, and durations of presentation.

A symbolic representation of the threshold values, the grayscale map, depicts an overall topographic impression of the visual field data by using darker symbols for low-sensitivity points and lighter symbols for high-sensitivity points. The computer program interpolates between tested points to provide a user-friendly picture (Fig 3-6). For clinical interpretation, the perimeter calculates for each value the statistical probability that the value falls outside the normal range among age-matched control subjects; the results are placed in a total-deviation plot. Optic neuropathy may cause substantial total-deviation depression with few or no pattern-deviation abnormalities. Because ocular media abnormalities (eg, refractive error, cataract) may depress the sensitivity of the entire visual field, the program produces a pattern-deviation plot by determining the sensitivity values for all points shifted (by the seventh-highest point) and reanalyzes them based on age-expected values. This reanalysis compensates for the overall sensitivity depression, allowing recognition of abnormal patterns (eg, scotomata, arcuate defects, homonymous defects) that might have been otherwise masked. Abnormal values are depicted topographically according to statistical probability: Darker squares represent higher probability, and lighter squares represent lower probability.

The long duration and repetitiveness of the original full-threshold perimetry test can fatigue patients, reducing the accuracy of the test results. Use of the Swedish interactive threshold algorithm (SITA) shortens the time needed to complete the full-threshold test by half but maintains the accuracy necessary for validity. (See BCSC Section 10, *Glaucoma*.)

The reliability of perimetry test results is assessed by identifying the following patient response characteristics:

- *false-positive response rate*: how frequently the patient signals when no target is displayed (The acceptable rate is typically <25% on threshold testing and <15% on SITA testing.)
- *false-negative response rate*: how often the patient fails to signal when a target brighter than the previously determined threshold for that spot is displayed (The acceptable rate is typically <25%, but the rate increases in regions of true visual field loss, because the patient is unable to reproduce responses accurately.)
- *fixation losses*: how often the patient identifies the stimulus in the previously plotted physiologic blind spot (an unexpected response), indicating that the eye is not aligned with the fixation target

Global indices are calculated to help determine changes in sensitivity over time. Such indices include a center-weighted mean of the sensitivity depressions across all points (ie,

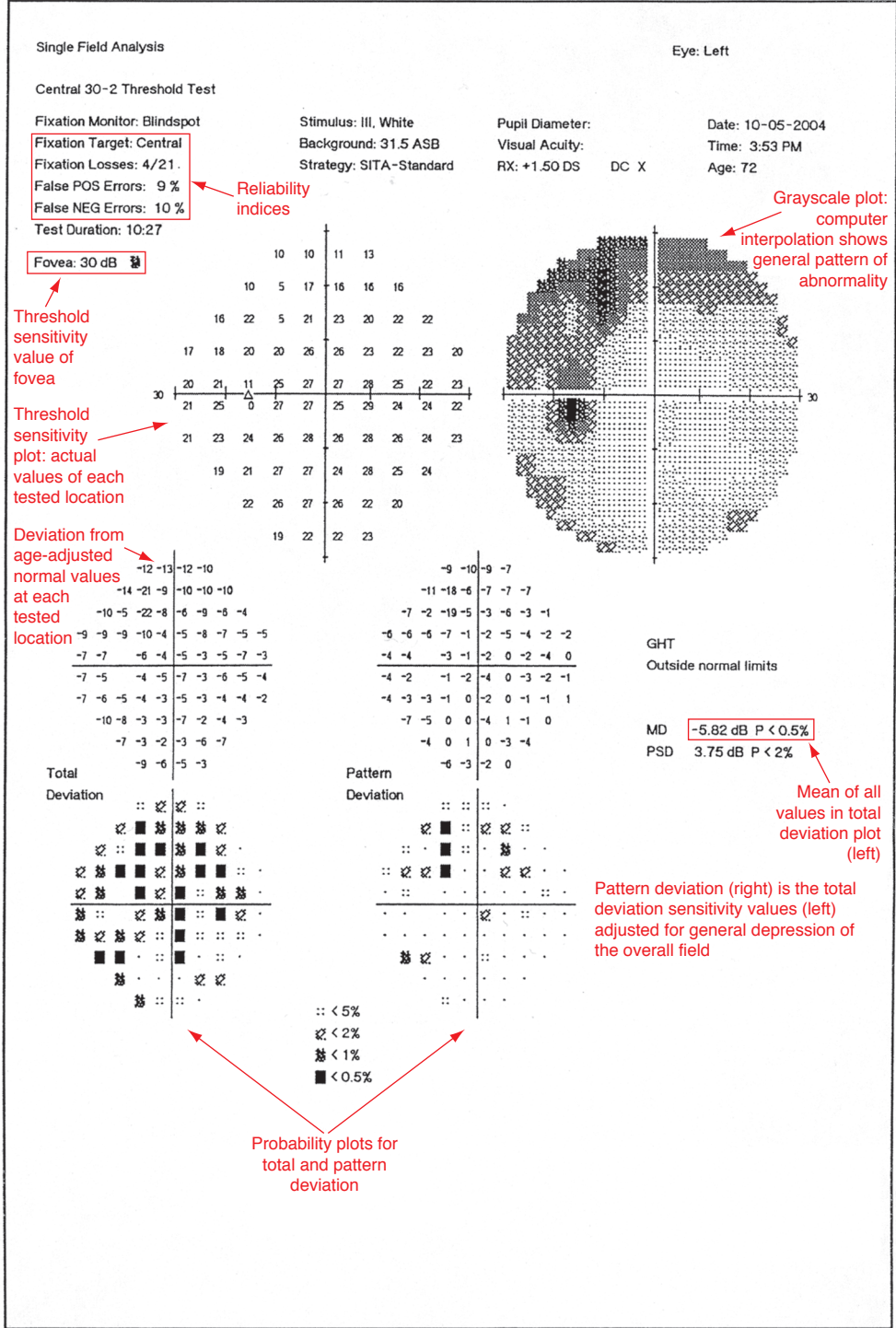


Figure 3-6 Report from a Humphrey 30-2 automated static perimetry program, with explanations of statistical analysis, grayscale, and probability plots (red type). (Courtesy of Anthony C. Arnold, MD.)

mean deviation) and different methods of addressing localized defects (eg, pattern standard deviation, corrected pattern deviation, loss variance).

Barton JJS, Benatar M. *Field of Vision: A Manual and Atlas of Perimetry*. Totowa (NJ): Humana Press; 2003.

Bettis DI, Johnson CA. Updated on automated perimetry. *Focal Points: Clinical Practice Perspectives*. San Francisco: American Academy of Ophthalmology; 2016, module 12.

Adjunct Testing

Contrast sensitivity testing

Whereas visual acuity testing uses targets that vary in size but have a single high level of contrast, contrast sensitivity testing uses targets with varying contrast levels. Two types of contrast sensitivity tests exist: (1) grating tests and (2) letter tests. Grating tests display rows of sine wave grating patches, each row reflecting a different spatial frequency. Grating tests, although arguably superior to letter tests, are difficult to administer and to reproduce reliably. The Pelli-Robson chart, which is commonly used for clinical letter testing, consists of letters of a fixed size that vary in contrast. The minimum level of contrast at which the letters can be detected is recorded.

Contrast sensitivity testing can detect and quantify vision loss in the presence of normal visual acuity. Such testing, however, is not specific for optic nerve dysfunction; media irregularities and macular lesions may also yield abnormal results. Interpretation of contrast sensitivity test data is more complex than interpretation of visual acuity data, particularly with regard to differentiating subtle abnormalities from normal presentation.

Contrast sensitivity testing is discussed further in BCSC Section 3, *Clinical Optics*, and Section 12, *Retina and Vitreous*.

Owsley C. Contrast sensitivity. *Ophthalmol Clin North Am*. 2003;16(2):171–177.

Photostress recovery testing

The photostress recovery test may help differentiate vision loss caused by a macular lesion or ocular ischemia from that caused by an optic neuropathy. CDVA is measured (a visual acuity of 20/80 or better is required). Tested monocularly, the patient gazes directly into a strong light held 2–3 cm from the eye for 10 seconds. As soon as possible after the light is removed, the patient attempts to read the next larger Snellen visual acuity line above the line representing the patient's CDVA (eg, a patient with a CDVA of 20/25 attempts to read the 20/30 line). Normal photostress recovery time is less than 30 seconds, but patients with maculopathy or severe carotid artery stenosis have prolonged recovery times, frequently 90–180 seconds or more. Patients with optic neuropathy maintain normal photostress recovery times.

Glaser JS, Savino PJ, Sumers KD, McDonald SA, Knighton RW. The photostress recovery test in the clinical assessment of visual function. *Am J Ophthalmol*. 1977;83(2):255–260.

Potential acuity meter testing

Potential acuity meter (PAM) testing can help determine whether media irregularities or opacities are the cause of decreased vision. Optotypes are projected onto the retina

through a dilated pupil, providing an estimate of best potential visual acuity. If the visual acuity does not improve to 20/20 with PAM, the ophthalmologist should search for a cause other than media opacities, such as optic neuropathy or maculopathy.

Reid O, Maberley DA, Hollands H. Comparison of the potential acuity meter and the visometer in cataract patients. *Eye*. 2007;21(2):195–199.

Fluorescein angiography

Fluorescein angiography may have a role in the investigation of some optic neuropathies. Angiographic leakage can differentiate true edema from pseudoedema of the ONH (the latter does not leak). Pseudoedema is characteristic of Leber hereditary optic neuropathy. Angiography may also demonstrate delayed or absent choroidal filling. This finding may explain vision loss due to choroidal ischemia, which strongly indicates a diagnosis of GCA (Fig 3-7). Indocyanine green (ICG) angiography may facilitate better assessment of choroidal blood flow and reveal deep inflammatory lesions. For further discussion of fluorescein angiography, see BCSC Section 12, *Retina and Vitreous*.

Lee AG, Brazis PW. Giant cell arteritis. *Focal Points: Clinical Modules for Ophthalmologists*. San Francisco: American Academy of Ophthalmology; 2005, module 6.

Fundus autofluorescence

Fundus autofluorescence uses the same excitation and emission filters as fluorescein angiography but does not require injection of a contrast dye. ONH drusen are visible with autofluorescence (Fig 3-8). Lipofuscin, which accumulates in higher amounts in



Figure 3-7 Fluorescein angiography image of a retina exhibiting signs of giant cell arteritis. Normally, the choroid fills completely within 3–5 seconds and before the retinal arteries do. The fluorescein dye appears light in this positive image. The retinal arteries and veins are filled, and the temporal choroid has a large perfusion defect consistent with choroidal ischemia from giant cell arteritis. (Reprinted with permission from Lee AG, Brazis PV. *Giant cell arteritis*. Focal Points: Clinical Modules for Ophthalmologists. San Francisco: American Academy of Ophthalmology; 2005, module 6. Cover image.)

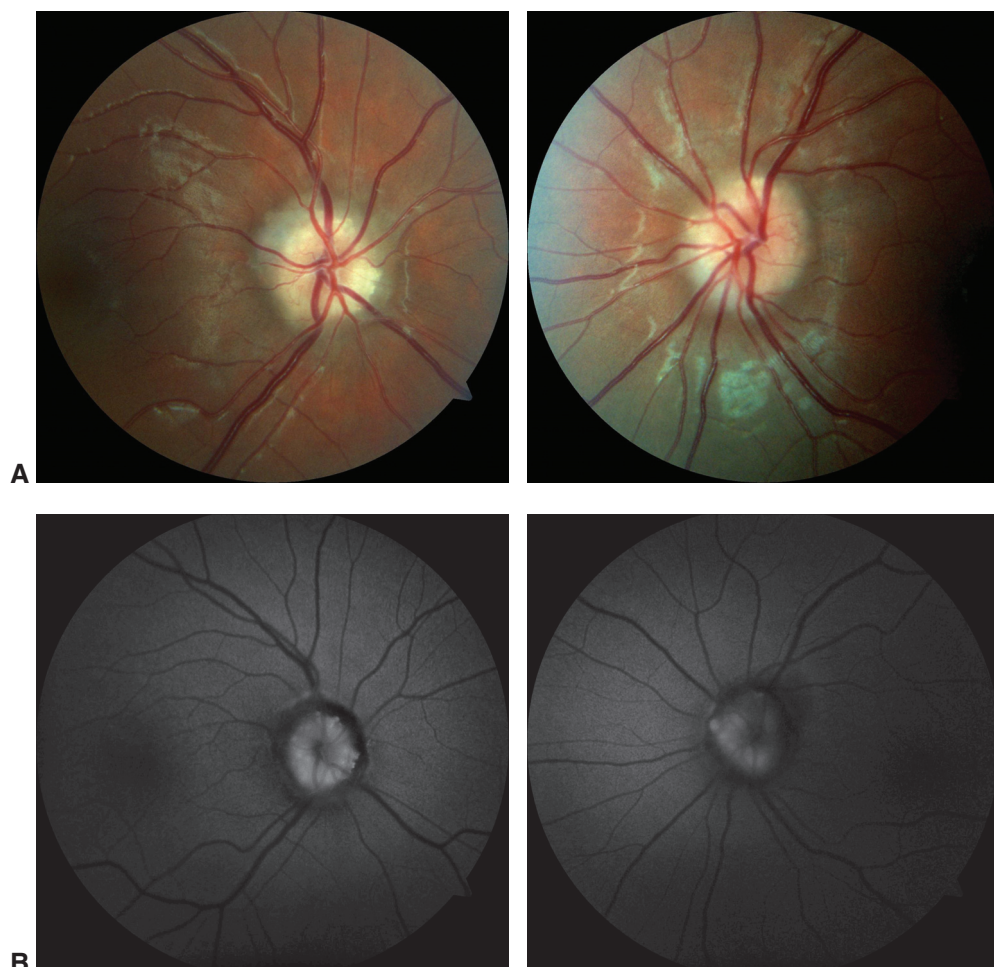


Figure 3-8 Investigation for idiopathic intracranial hypertension. **A**, ONH photograph demonstrates blurring of the ONH margins with elevation, suggesting possibly bilateral ONH swelling (ie, papilledema). **B**, ONH drusen are visible with fundus autofluorescence, consistent with pseudopapilledema. (Courtesy of Helen V. Danesh-Meyer, MD.)

damaged retinal pigment epithelium (RPE) cells, causes hyperfluorescence. This is seen in some retinal pathologies, such as multiple evanescent white dot syndrome (MEWDS), acute macular neuroretinopathy (AMN), acute zonal occult outer retinopathy (AZOOR), and acute idiopathic blind-spot enlargement (AIBSE). Because fundusoscopic abnormalities in these conditions are often subtle, they are commonly mistaken for an optic neuropathy, which makes fundus autofluorescence a valuable diagnostic tool in this clinical setting.

Optical coherence tomography

Optical coherence tomography (OCT) provides noninvasive, high-resolution, in situ visualization of the retinal layers and ONH. OCT can be very helpful in the evaluation and management of certain neuro-ophthalmic conditions. OCT is useful for structural

measurement of peripapillary RNFL thickness, volumetric analysis of the ONH, and evaluation of macular anatomy. The measurement of the RNFL thickness provides indirect information regarding the axonal integrity of the optic nerve. In several optic neuropathies, the degree and the site of RNFL thinning correlate with the threshold sensitivity of the corresponding area of the visual field (Figs 3-9, 3-10).

OCT predicts the potential for visual recovery after surgery in patients with compressive chiasmal tumors. Patients who have significant visual field defects but preserved RNFL thickness (the threshold is approximately 75 μm but depends on age) typically recover excellently, irrespective of the degree of preoperative vision loss.

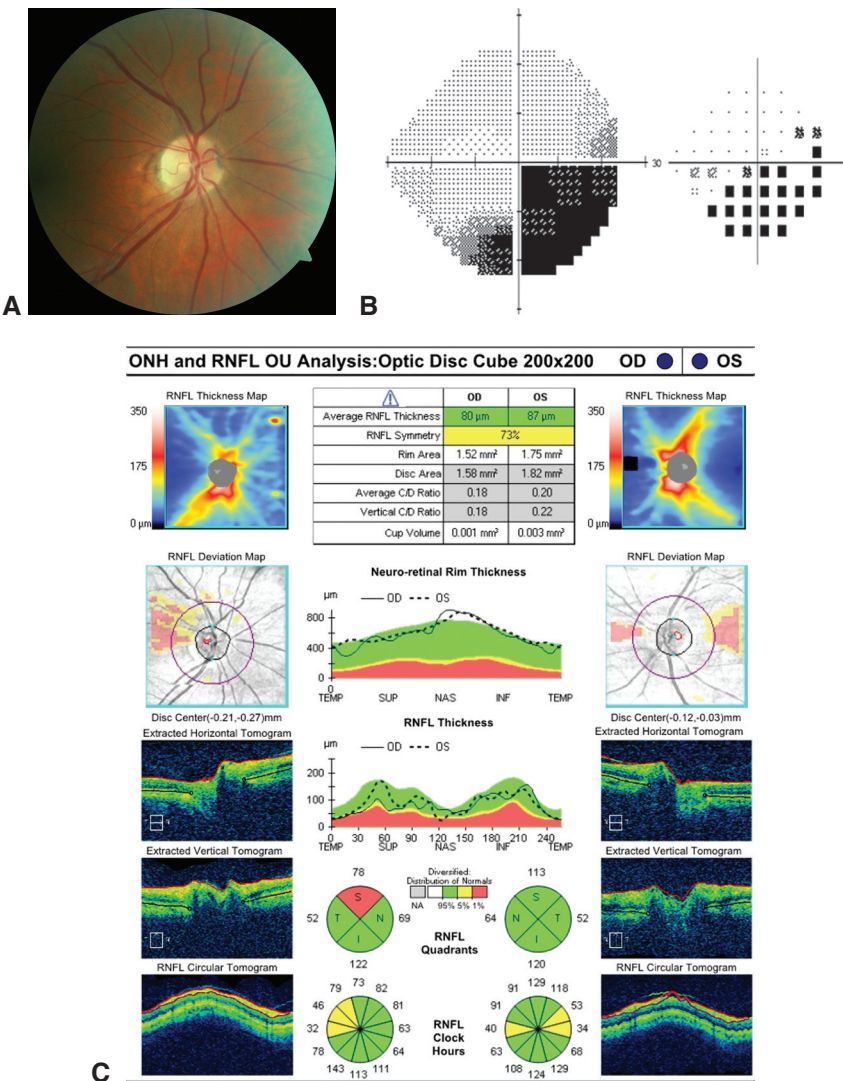


Figure 3-9 Superior sectoral ONH pallor following nonarteritic anterior ischemic optic neuropathy, right eye. **A**, ONH photograph. **B**, The corresponding static automated perimetry demonstrates an inferior scotoma. **C**, Optical coherence tomography (OCT) demonstrates superior RNFL thinning. (Courtesy of Helen V. Danesh-Meyer, MD.)

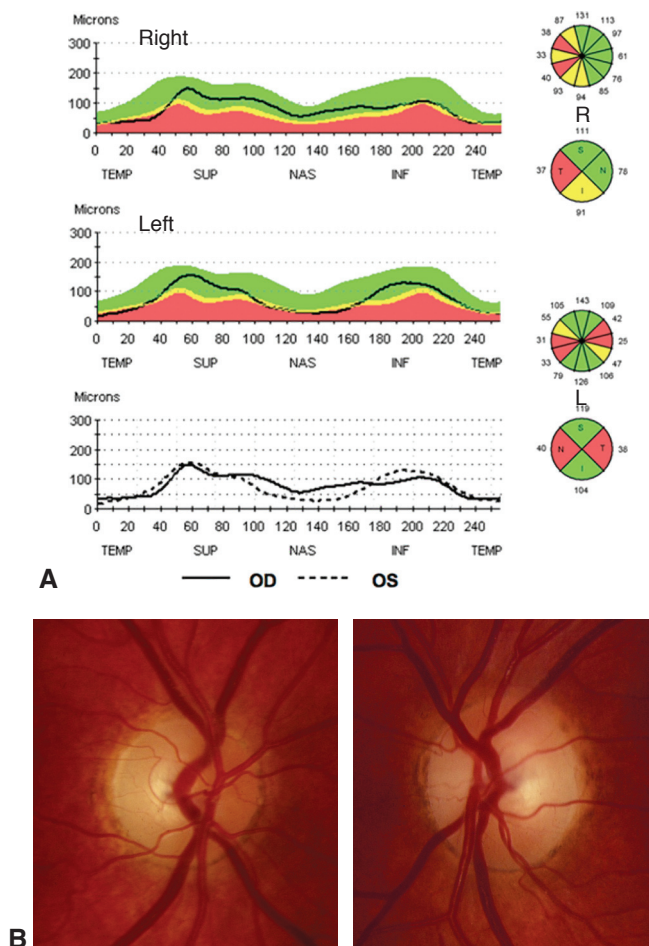


Figure 3-10 Pituitary adenoma with bitemporal visual field loss. OCT demonstrates nasal and temporal thinning of the retinal nerve fiber layer (RNFL) (**A**), which corresponds to the clinical appearance of horizontal band atrophy (**B**). (Courtesy of Helen V. Danesh-Meyer, MD.)

Automatic segmentation of the macula on OCT allows measurement of the inner retina (RNFL, ganglion cell layer, and inner plexiform layers), referred to as the *ganglion cell complex* (GCC). In patients with multiple sclerosis (MS) or other optic neuropathies, GCC thickness better correlates with visual acuity and quality of life than does RNFL thickness.

Macular cube OCT and macular line scans can help identify occult retinal pathology that mimics optic nerve disease. For example, subretinal fluid from central serous retinopathy may be mistaken for optic neuritis. MEWDS, AZOOR, and AMN can be detected with OCT owing to the disruption of the inner and outer segments of the retina (Fig 3-11).

OCT also has a role in monitoring disease progression. As in glaucoma, the RNFL thickness can be monitored over time in patients with chronic diseases such as MS and compressive optic neuropathy to quantify axonal loss (Fig 3-12).

A clinical challenge often encountered in neuro-ophthalmology is differentiation among anomalous optic nerves, ONH drusen, and papilledema. Several OCT features

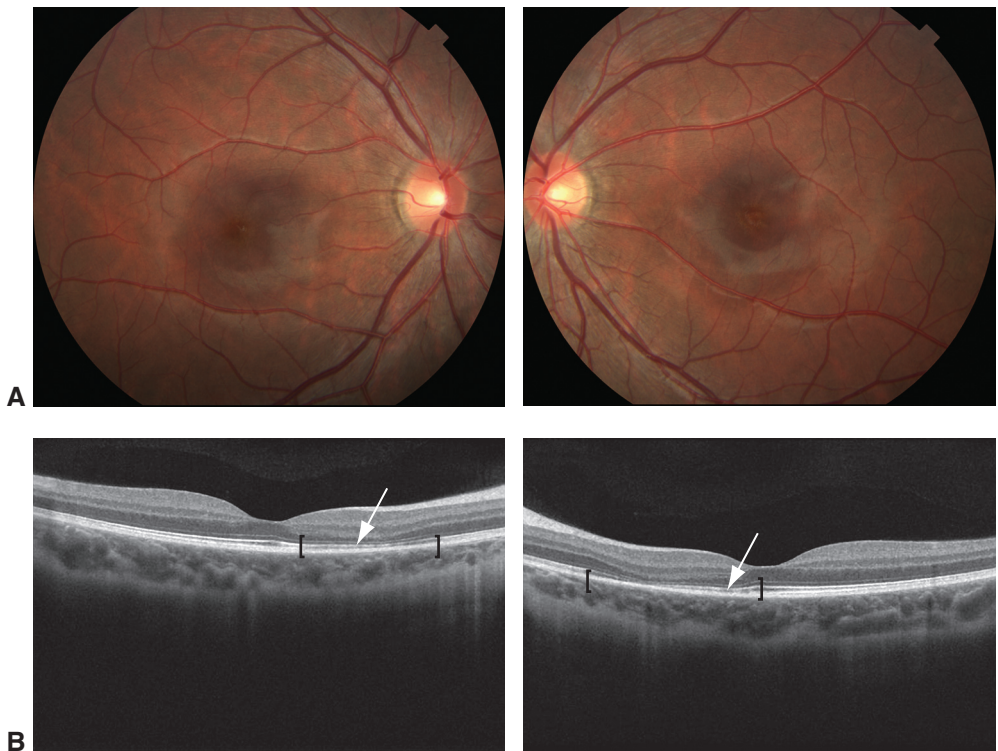


Figure 3-11 Acute macular neuroretinopathy (AMN) in a 16-year-old male who presented with vision loss in both eyes. **A**, Fundus photographs reveal mild macular changes. **B**, Corresponding macular OCT line scans demonstrate the area of disruption (brackets) of the photoreceptor inner segment (IS)/outer segment (OS) junction (arrows) in the nasal macula of each eye. (Reprinted with permission from Sitko KR, Athappilly G, Hedges TR III. Ancillary testing in neuro-ophthalmology. Focal Points: Clinical Modules for Ophthalmologists. San Francisco: American Academy of Ophthalmology; 2015, module 1.)

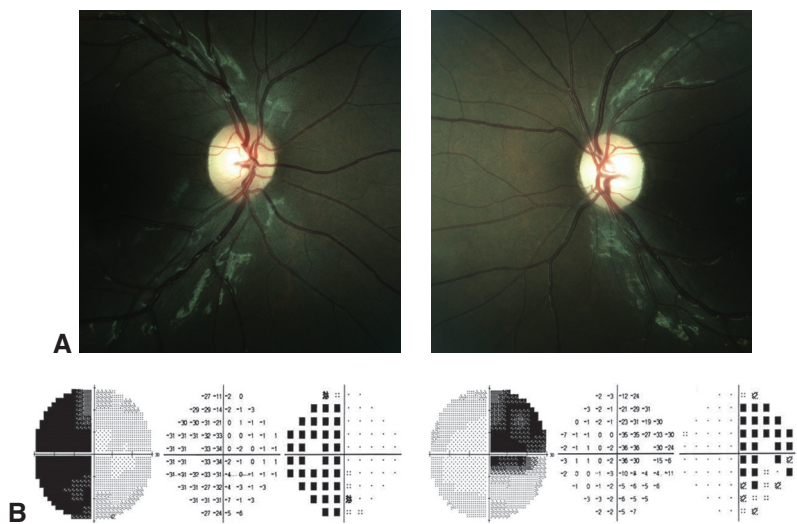


Figure 3-12 Evaluation of a patient with a pituitary tumor. **A**, Bilateral ONH pallor. **B**, The pre-operative visual field demonstrates bitemporal hemianopia.

(Continued)

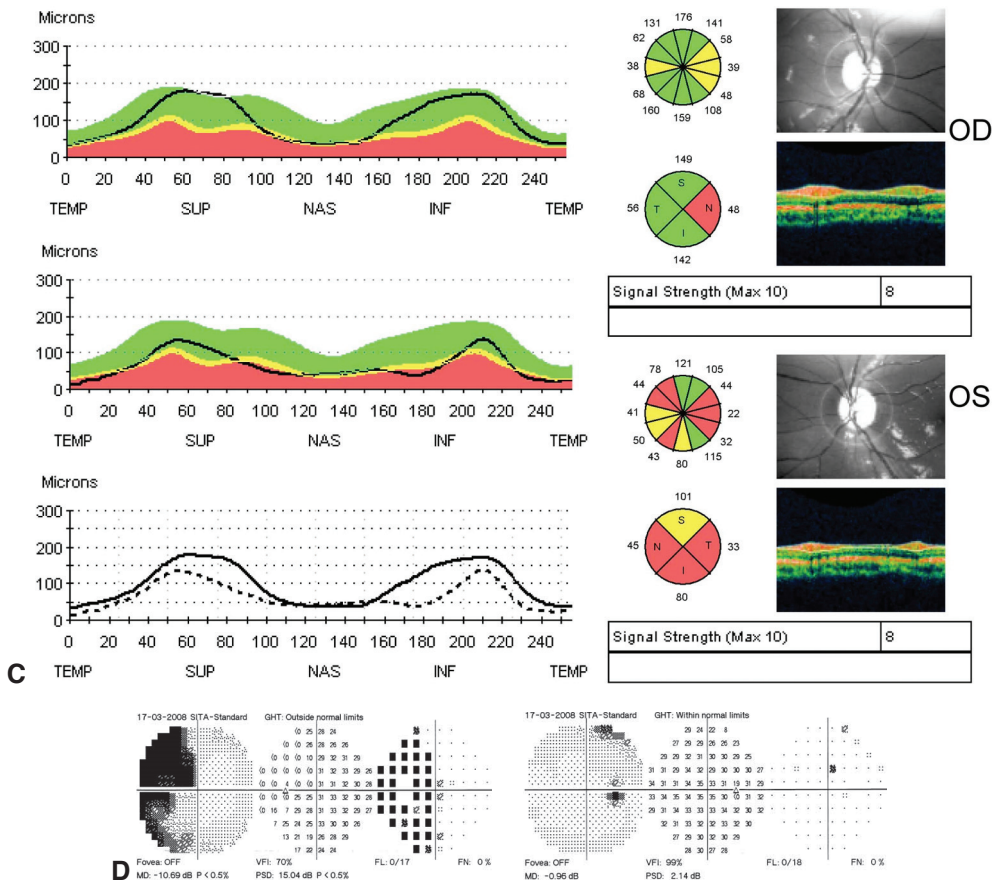


Figure 3-12 (continued) C, OCT shows minor nasal thinning on the right, with a normal average RNFL thickness of 99 μm . The left shows generalized thinning, with disproportionate thinning nasally and temporally, and an average thickness of 67 μm . The thin RNFL on the left (because it is <75 μm) suggests a poor recovery, while a normal preoperative RNFL suggests significant recovery of visual field to normal/near-normal levels. **D,** The postoperative visual field defect shows near-normal resolution of the temporal visual field on the right and persistent temporal defect on the left. (Courtesy of Helen V. Danesh-Meyer, MD.)

may suggest the diagnosis; however, OCT currently cannot definitively distinguish mild papilledema from an anomalous, crowded ONH or buried ONH drusen.

OCT has limitations. Many of the abnormalities seen on OCT are not specific to a particular disease process. For example, thinning of the RNFL occurs with any optic neuropathy. RNFL loss plateaus around 40–50 μm ; further loss is undetectable. The wide variability in RNFL values means that some patients have statistically abnormal results that are in fact normal for them. See BCSC Section 10, *Glaucoma*, and Section 12, *Retina and Vitreous*, for more information.

Kardon RH. Role of the macular optical coherence tomography scan in neuro-ophthalmology. *J Neuroophthalmol.* 2011;31(4):353–361.

Mendoza-Santesteban CE, Gonzalez-Garcia A, Hedges TR III, et al. Optical coherence tomography for neuro-ophthalmologic diagnoses. *Semin Ophthalmol.* 2010;25(4):144–154.

Ultrasonography

Ultrasonography is useful in diagnosing buried ONH drusen, which are hyperechoic on B-scan. Ultrasonography is more sensitive for ONH drusen than is autofluorescence or computed tomography. Ultrasound is also helpful in diagnosing scleritis, which can mimic optic neuritis. Patients with papilledema can have a positive 30° test, in which the diameter of the optic nerve sheath decreases when the patient is asked to fixate 30° away from primary gaze.

Electrophysiologic testing

When the patient has central or peripheral vision loss but no obvious fundus abnormality, ancillary electrophysiologic testing may help confirm or rule out occult abnormalities of the optic nerve or retinal function. See BCSC Section 12, *Retina and Vitreous*.

Visual evoked potential testing Visual evoked potential (VEP) testing measures electrical signals produced in response to a visual stimulus; the signals are recorded at the scalp overlying the occipital cortex. Damage anywhere along the afferent visual pathway can reduce the amplitude or speed of the signal. Because the central visual field predominates in the occipital cortex, isolated peripheral vision loss may yield normal VEP results.

The most common stimulus used for VEP testing is a checkerboard target with a pattern that reverses every half-second. The pattern size may also vary, with smaller pattern sizes allowing detection of smaller changes in function. If patients with poor vision cannot easily see a pattern stimulus, a flash stimulus may be used instead. The response from the checkerboard pattern provides a more quantifiable and reliable VEP waveform.

The most common wave measured in VEP testing is the P100 wave, which occurs 100 milliseconds after stimulus onset in patients with normal vision. The P100 *latency* and, to a lesser degree, the *amplitude* are the most useful features analyzed. Demyelination has a greater effect on the latency of the P100 waveform than on its amplitude. Ischemic, compressive, or toxic optic nerve damage primarily reduces amplitude, with less effect on latency. A normal VEP (especially in response to a checkerboard pattern stimulus with a high spatial frequency) is evidence for a nonorganic etiology in a patient who reports severe vision loss. However, an abnormal VEP does not prove pathology.

The VEP test has significant limitations. It is subject to influence by numerous factors that may produce abnormal waveforms despite normal visual pathways, including uncorrected refractive error, media opacities, amblyopia, fatigue, and inattention (intentional or unintentional). Although an abnormal VEP may indicate visual pathway dysfunction, the differential effects on latency versus amplitude may not be sensitive or specific enough to narrow the differential diagnosis. The VEP is clinically useful in 2 situations: (1) evaluation of the visual pathway in an inarticulate patient and (2) confirmation of intact visual pathways in a patient with suspected nonorganic disease. A consistently abnormal flash response in an infant or inarticulate adult reflects gross impairment. An abnormal pattern response may indicate damage or may be a false-negative result for the reasons just cited. Normal responses confirm intact visual pathways.

Odom JV, Bach M, Brigell M, et al; International Society for Clinical Electrophysiology of Vision. ISCEV standard for clinical visual evoked potentials: (2016 update). *Doc Ophthalmol*. 2016;133(1):1–9.

Electroretinography The electroretinogram (ERG) measures the electrical activity of the retina in response to various light stimuli under different states of light adaptation. Electrical activity is measured at the corneal surface by electrodes embedded in a corneal contact lens worn for testing.

The full-field ERG response is generated by stimulating the entire retina with a light source under varying conditions of retinal adaptation. Major components of the electrical waveform that are generated and measured include the *a-wave*, derived primarily from the photoreceptor layer; the *b-wave*, derived from the inner retina, probably Müller and on-bipolar cells; and the *c-wave*, derived from the RPE and photoreceptors. The examiner can separate rod and cone photoreceptor responses by varying the stimuli and the state of retinal adaptation during testing.

The ERG is useful in detecting diffuse retinal disease in cases of generalized or peripheral vision loss. Disorders such as retinitis pigmentosa (including the forms without pigmentation), cone-rod dystrophy, toxic retinopathies, and the retinal paraneoplastic syndromes (cancer-associated retinopathy [CAR]) and melanoma-associated retinopathy [MAR]) may present with variably severe vision loss and minimal visible ocular abnormality. Invariably, the ERG pattern is severely depressed by the time substantial vision loss has occurred, and thus testing is extremely useful. The full-field test, however, measures only a mass response of the entire retina; minor or localized retinal disease, particularly maculopathy, even with severe visual acuity loss, might not produce an abnormal response.

The *multifocal ERG* (mfERG) simultaneously records and topographically maps ERG signals from up to 250 focal retinal locations within the central 30° (Fig 3-13). Because it is a light-adapted test, an mfERG tests the cone system. Further, because it does not rely on a mass retinal response, as does a full-field ERG, an mfERG is very useful in detecting

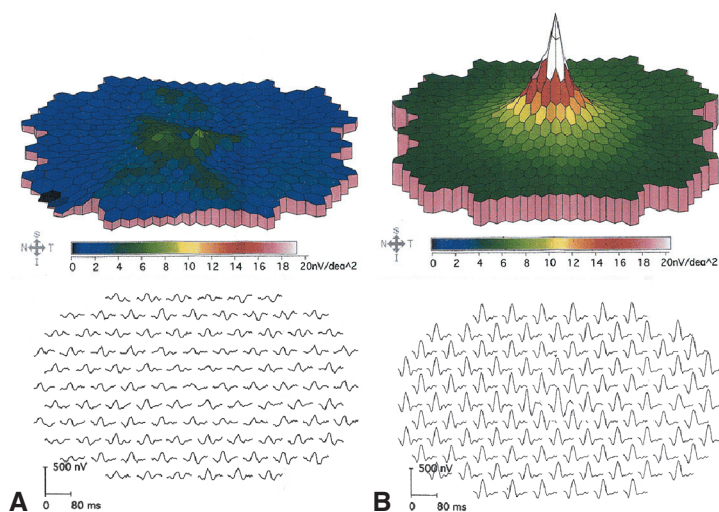


Figure 3-13 Multifocal electroretinogram response of a patient with maculopathy. The pattern of the affected eye (**A**) shows flattening of the foveal waveforms compared with that of the unaffected eye (**B**). (Courtesy of Anthony C. Arnold, MD.)

occult focal retinal abnormalities, especially early cone and cone-rod dystrophies. This technique can differentiate optic nerve from macular disease in occult central vision loss, because the signal generally remains normal in optic nerve disease. Also, causes of outer retinal degeneration, such as MEWDS, AIBSE, and AZOOR, result in changes in the mfERG. See BCSC Section 12, *Retina and Vitreous*.

Holder GE, Gale RP, Acheson JF, Robson AG. Electrodiagnostic assessment in optic nerve disease. *Curr Opin Neurol*. 2009;22(1):3–10.

Hood DC, Odel JG, Chen CS, Winn BJ. The multifocal electroretinogram. *J Neuroophthalmol*. 2003;23(3):225–235.

The Patient With Decreased Vision: Classification and Management

The initial goal in the assessment of reduced vision in any patient is to localize the cause of vision loss to a specific part of the visual pathway(s). Decreased vision may arise from refractive errors or abnormalities in the ocular media, retina, optic nerve, optic tracts, visual radiations, and occipital cortex. Evaluation of the patient with vision loss requires consideration of the clinical history together with results of the examination and ancillary testing, as outlined in Chapter 3, to determine causation and management.

Ocular Media Abnormality

Irregularities or opacities of the ocular media tend to reduce visual acuity, but they do not affect pupils, color vision, or the appearance of the posterior pole. Corneal disease such as dry eye or epithelial basement membrane dystrophy, as well as lenticular abnormalities, may be identified by careful slit-lamp examination. These conditions may cause generalized reduction of sensitivity on automated perimetry testing. These conditions may be subtle enough to be missed during a cursory ophthalmic examination; they may be diagnosed only during a thorough neuro-ophthalmologic evaluation in patients with presumed unexplained vision loss.

Retinopathy

Maculopathies can mimic an optic neuropathy (Table 4-1). They can produce decreased visual acuity and central visual field loss with variable color vision loss. However, unless there is extensive retinal abnormality, relative afferent pupillary defect (RAPD) in maculopathies is usually not present. Maculopathy tends to cause parallel losses in color discrimination and visual acuity, unlike optic nerve disease, which may cause a disproportionately greater loss in color vision than in visual acuity, particularly if the disease is inflammatory or compressive. The exception is cone dystrophy, in which there is relatively unimpaired central visual acuity in patients experiencing severe color impairment.

Table 4-1 Clinical Distinction Between Optic Neuropathy and Maculopathy

Clinical Finding	Optic Neuropathy	Maculopathy
Symptom		
Metamorphopsia	Rare	Common
Pain	Common in optic neuritis	None
Photophobia/glare	Rare	Sometimes
Photopsia	Rare	Common
Sign		
Amsler grid finding	Absent lines (scotoma)	Distorted lines
Funduscopy findings	Normal, pale, or swollen ONH Macula normal	Normal or pale ONH Macula normal, edematous, or abnormal
Photostress testing	Normal	Delayed
Reduced visual acuity	Common	Common
Relative afferent pupillary defect	Present if unilateral or bilateral asymmetric	None, unless there is extensive retinal damage
Visual field defect	Central scotoma, nerve bundle defect	Central scotoma

ONH = optic nerve head.

Visual field deficits in maculopathy tend to be focal and central, whereas deficits in optic neuropathies tend to be larger, often cecentral, and part of a generalized depression of visual field sensitivity. Metamorphopsia almost always has a macular origin and is a symptom of optic neuropathies only in rare cases. In general, maculopathies produce visible fundus abnormalities that can aid correct diagnosis but that, when subtle, can be mistaken for optic neuropathy. Optical coherence tomography (OCT), autofluorescence imaging of the macula, fluorescein angiography, and multifocal electroretinography (ERG) may help detect an abnormality in retinal structure or function. (See Chapter 3 and BCSC Section 12, *Retina and Vitreous*, for further discussion of these imaging techniques.)

Common maculopathies and retinopathies that are often mistaken for optic nerve disease include acute idiopathic blind-spot enlargement (AIBSE) and acute zonal occult outer retinopathy (AZOOR), both of which overlap with multiple evanescent white dot syndrome (MEWDS), as well as cone dystrophy. Patients with these entities may present with normal funduscopy findings. Rarer entities include cancer-associated retinopathy and melanoma-associated retinopathy. Other retinal disorders that may be mistaken for optic neuropathies include central serous chorioretinopathy and cystoid macular edema (these disorders are discussed in detail in BCSC Section 12, *Retina and Vitreous*).

Acute Idiopathic Blind-Spot Enlargement, Acute Zonal Occult Outer Retinopathy, and Multiple Evanescent White Dot Syndrome

Traditionally, enlargement of the blind spot (Fig 4-1) on visual field testing is associated with changes of the optic nerve head (ONH) such as edema or tilting. However, the term

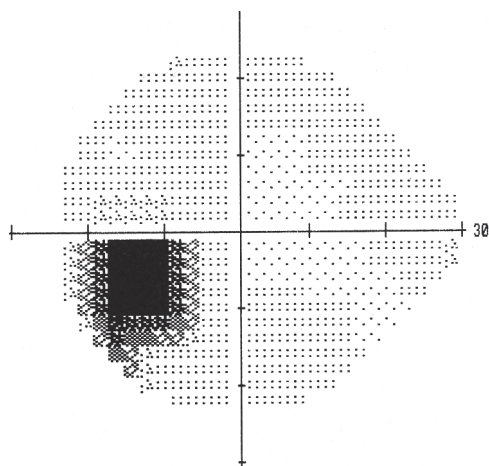


Figure 4-1 Enlargement of the blind spot in the left eye, as shown on Humphrey 24-2 perimetry. A 32-year-old woman presented with a 6-month history of continuously flashing lights to the left side in her left eye. Visual acuity was 20/15 bilaterally with a $<0.3\text{-log}_{10}$ unit left afferent pupillary defect. Results of automated quantitative perimetry show enlargement of the physiologic blind spot. This temporal defect does not respect the vertical midline. (Courtesy of Michael S. Lee, MD.)

AIBSE describes a clinical syndrome in which the prominent visual symptom is a monocular scotoma, often temporal in location and associated with photopsias. The main finding is an enlarged blind spot. The fundus may appear normal or show evidence of ONH edema, peripapillary retinal lesions, choroiditis, changes in the retinal pigment epithelium (RPE), or uveitis.

The term *AZOOR* is used to describe a syndrome similar to *AIBSE* but with more extensive retinal changes. This variability has led to controversy over whether these entities are separate or a spectrum of 1 disorder. *MEWDS* exemplifies this controversy. Fundus examination may reveal characteristic small, deep retinal white spots in the posterior retina that usually last for weeks and resolve spontaneously. The transient nature of the lesions could explain the normal retinal appearance at first examination. Photopsias are a prominent symptom thought to reflect disease of the outer retina. Fluorescein angiography and indocyanine angiography are often abnormal. Multifocal ERG shows depression in the peripapillary region, whereas a full-field ERG response may demonstrate depressed a-waves or substantial intereye asymmetry. Spectral-domain OCT may reveal attenuation of the outer layers.

Although *AIBSE*, *AZOOR*, and *MEWDS* represent outer retinal disorders, patients with these conditions may have a small RAPD. In general, patients with these disorders have a good visual prognosis. (See BCSC Section 9, *Uveitis and Ocular Inflammation*, and Section 12, *Retina and Vitreous*, for further discussion.)

Gross NE, Yannuzzi LA, Freund KB, Spaide RF, Amato GP, Sigal R. Multiple evanescent white dot syndrome. *Arch Ophthalmol*. 2006;124(4):493–500.

Jampol LM, Wiredu A. MEWDS, MFC, PIC, AMN, AIBSE, and AZOOR: one disease or many? *Retina*. 1995;15(5):373–378.

Monson DM, Smith JR. Acute zonal occult outer retinopathy. *Surv Ophthalmol*. 2011;56(1):23–35.

Volpe NJ, Rizzo JF III, Lessell S. Acute idiopathic blind spot enlargement syndrome. A review of 27 new cases. *Arch Ophthalmol*. 2001;119(1):59–63.

Cone Dystrophy

Cone dystrophy is a rare disorder characterized by vision loss that may be mistaken for a bilateral optic neuropathy. Patients of any age can present with a gradually progressive decline in visual acuity and color vision. Photophobia and hemeralopia (“day blindness”) are common. In the early stages, the fundus can appear normal or show a slightly blunted foveal reflex with granular macular pigmentation. As the disease progresses, the macular RPE becomes atrophic in a central oval region. A “bull’s-eye” pattern of depigmentation may be present. Fluorescein angiography and fundus autofluorescence may reveal these abnormalities before they become clinically apparent. Full-field ERG results may be normal initially but eventually show markedly depressed photopic (cone) response and less prominently affected scotopic (rod) response. Multifocal ERG studies show central depression. OCT scans may show thinning of outer macular layers, loss of the ellipsoid zone, and outer cavitation.

Autoimmune Retinopathies and Paraneoplastic Retinopathies

Cancer-associated retinopathy

Cancer-associated retinopathy (CAR) presents with bilateral progressive vision loss (which may be unilateral or asymmetric in onset) and impaired color vision. Associated symptoms include photopsias, nyctalopia (night blindness), impaired dark adaptation, ring scotoma, and peripheral and/or central visual field loss. Symptoms progressively worsen over weeks to months, often before the underlying malignancy is identified. The most common cause is small-cell lung carcinoma, although other lung, breast, uterine, and cervical malignancies have been reported. The fundus may initially appear normal, but the ERG response shows markedly reduced amplitudes. As the disease progresses, the retinal arterioles become attenuated, the RPE thinned and mottled, and the ONHs atrophic. Vision loss is typically severe. When CAR is suspected, the patient should be tested for the presence of antibodies against retinal proteins (ideally by both Western blot and immunohistochemical analysis). Serum antiretinal antibody testing is now commercially available. However, antibodies against recoverin, the best-characterized antibody, are found in only a minority of patients with CAR. If clinical suspicion of CAR remains high but the antibody testing is negative, the ophthalmologist should look for an underlying cancer. Empiric treatment with various combinations of corticosteroids, plasmapheresis, and intravenous immunoglobulin has been reported; in general, however, the prognosis for vision is poor.

Melanoma-associated retinopathy

Melanoma-associated retinopathy (MAR) is a rare syndrome that involves primarily rod bipolar cells, with corresponding symptoms of photopsia, nyctalopia, and bilateral peripheral visual field loss. MAR usually develops rapidly over weeks to months but may have a sudden onset. Visual symptoms typically develop in patients with previously diagnosed melanoma. Visual acuity, color vision, and the central visual field are often initially normal with prominent peripheral visual field loss. The fundus may appear normal, or it may show RPE irregularity, retinal arteriolar attenuation, or ONH pallor. Full-field

ERG response shows rod dysfunction. The multifocal ERG pattern is relatively preserved; MAR affects rod function, and the multifocal ERG measures photopic responses. Unlike CAR, visual function may remain stable and nonprogressive in MAR. No treatment has proven effective, but anecdotal success with intravenous immunoglobulin has been reported.

Braithwaite T, Holder GE, Lee RW, Plant GT, Tufail A. Diagnostic features of the autoimmune retinopathies. *Autoimmun Rev*. 2014;13(4–5):534–538.

Gordon LK. Paraneoplastic syndromes in neuro-ophthalmology. *J Neuroophthalmol*. 2015; 35(3):306–314.

Nonparaneoplastic autoimmune retinopathy

Nonparaneoplastic autoimmune retinopathy (NpAIR) has a more variable presentation that may include decreased visual acuity, peripheral visual field loss, positive visual phenomenon, or nyctalopia. NpAIR is associated with autoimmune disease in approximately 50% of patients. ERG findings are highly variable but usually demonstrate cone-system dysfunction, either macular or generalized, with postphototransduction involvement. The clinician should diagnose NpAIR only following comprehensive systemic investigation to exclude occult malignancy. NpAIR-associated antibody targets overlap with those of CAR, with the exception of recoverin, which has not been reported in NpAIR to date.

Optic Neuropathy

Clinically, patients with optic neuropathies typically present with visual acuity loss, visual field loss, dyschromatopsia, and an RAPD (in patients with unilateral or asymmetric damage). The ONH may appear normal or acutely swollen; optic atrophy (optic nerve pallor) typically develops 4–6 weeks later, even after vision has recovered.

Visual Field Patterns in Optic Neuropathy

Retinal ganglion cell nerve fibers enter the ONH in 3 major groups (Fig 4-2). Thus, visual field loss attributable to lesions of the optic nerve may be associated with 3 types of fibers (Table 4-2):

1. *papillomacular fibers*: cecocentral scotoma (Fig 4-3A, left panel), paracentral scotoma (Fig 4-3A, right panel), and central scotoma (Fig 4-3B)
2. *arcuate fibers*: arcuate scotoma (nerve fiber bundle defect) (Fig 4-3C), altitudinal defect (broader region of arcuate fibers) (Fig 4-3D), and nasal (step) defect (temporal portion of arcuate fibers) (Fig 4-3E). These fibers align along the temporal horizontal retinal raphe; damage to them produces defects that do not cross and respect the nasal horizontal meridian
3. *nasal radiating fibers*: temporal wedge defect

Blind-spot enlargement results from ONH edema of any cause, due to displacement of the peripapillary retina (Fig 4-3F).

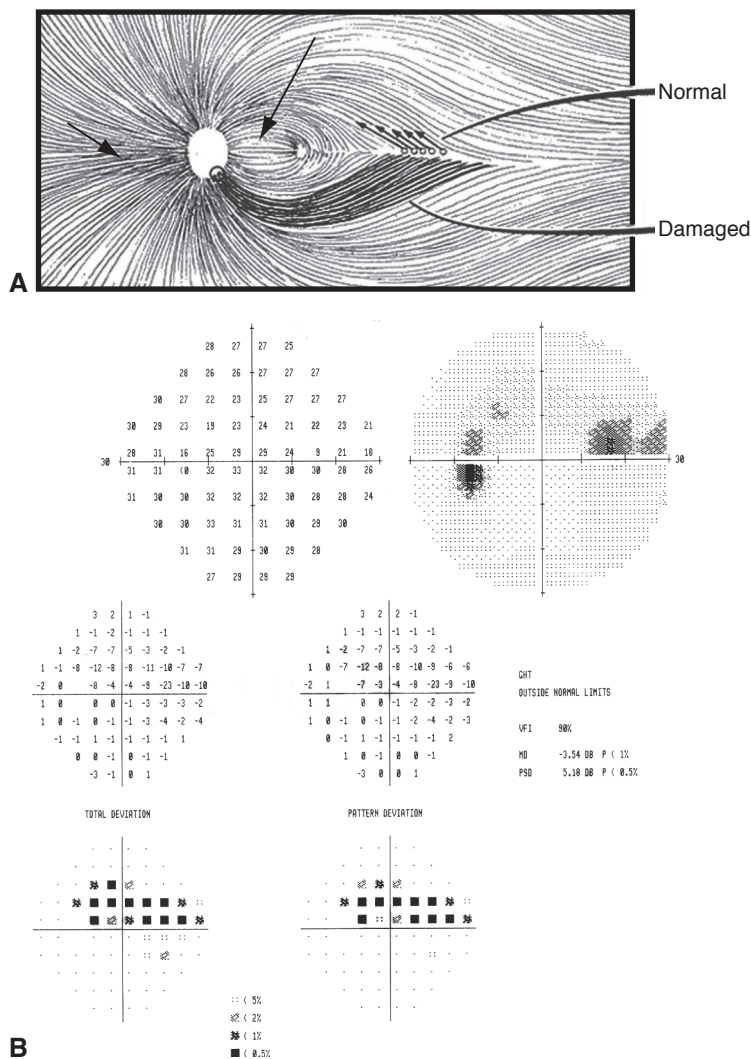


Figure 4-2 Retinal ganglion cell nerve fibers. **A**, Schematic representation of retinal nerve fiber layer entering the optic nerve head (ONH). The fibers are classified as arcuate (*inferior bundle highlighted*), papillomacular (*long arrow*), and nasal radiating (*short arrow*). **B**, Humphrey 30-2 perimetry grayscale diagram of the left eye, showing superior arcuate visual field defect corresponding to the inferior arcuate nerve fiber bundle (*damage highlighted*). (Part B courtesy of Michael S. Lee, MD.)

Causes of Optic Neuropathy

Optic neuropathies may be classified as anterior (with ONH edema) or posterior (with a normal-appearing ONH at onset). When evaluating a patient with an optic neuropathy, it is best to consider the possible mechanisms of optic neuropathies (Table 4-3). Clinical characteristics such as the patient’s age, mode of onset, laterality, presence of pain, color vision, type of visual field defects, optic nerve appearance, and results of orbital magnetic resonance imaging (MRI) are very helpful in determining the underlying cause of the optic neuropathy.

Table 4-2 Glossary of Perimetric Terms

Term	Characteristics
Characteristics of the visual field defect	
Absolute	No stimulus perceived in the affected area
Relative	Bigger and brighter stimuli may be perceived in the affected field, but smaller, dimmer targets are not seen. The size and shape of the visual field defect, therefore, change inversely with changes in size and/or intensity of the presented stimulus. Defects may be described as shallow when only the smallest or dimmest targets fail to be identified or deep if bright objects are not detected in the central portion of the defect.
Terms describing visual field defects	
Scotoma	Area of depressed visual function surrounded by normal visual function (eg, the blind spot) (see Fig 4-3A)
Central	Involves fixation only (see Fig 4-3B)
Cecocentral	Extends from fixation temporally to the blind spot (see Fig 4-3A, left panel)
Paracentral	Involves a region next to, but not including, fixation (see Fig 4-3A, right panel)
Pericentral	Involves a region symmetrically surrounding, but not involving, fixation
Arcuate	Corresponds to and represents nerve fiber bundle loss (see Fig 4-3C)
Altitudinal	A more extensive arcuate defect involving 2 quadrants in either the superior or inferior field (see Fig 4-3D)
Quadrantanopia	One quadrant of visual field involved
Hemianopia	One-half of visual field involved, either nasal or temporal (see Fig 4-25)
Description of bilateral visual field defects with respect to spatial localization and extent	
Homonymous	Same side of visual space affected in each eye (see Fig 4-25)
Bitemporal	Opposite temporal sides of visual field space affected in each eye (see Fig 4-25)
Complete	Entire field affected
Incomplete	A portion of the field spared (see Fig 4-25)
Congruous	Tendency for homonymous field defect to be symmetric (ie, to have a similar size, location, and shape in each eye's field)

Biousse V, Newman NJ. Optic neuropathies. In: *Neuro-Ophthalmology Illustrated*. 2nd ed. New York: Thieme; 2015:179–244.

Papilledema

Papilledema refers to ONH edema resulting from increased intracranial pressure (ICP). On ophthalmoscopy, papilledema is indistinguishable from other causes of ONH edema. Acute papilledema produces hyperemia of the ONH, with dilation of the existing ONH surface capillary net and telangiectasia of the surface and radial peripapillary vessels. The edematous peripapillary retinal nerve fiber layer (RNFL) is grayish white and opalescent, with feathered, striated margins that obscure the ONH edge and the retinal vessels coursing through it. Early papilledema begins at the superior and inferior poles of the ONH. As papilledema worsens, it encompasses the nasal ONH, creating a C-shaped area of ONH edema with the opening along the temporal rim. The edema eventually involves the entire ONH and causes blurring of major vessels off the ONH head. Late findings include absence of the physiologic cup and obscuration of vessels on the ONH itself. Absence of spontaneous venous pulsations may reflect increased ICP, but absence at initial examination is of limited value; 20% of the general population have no spontaneous venous pulsations. The disappearance of these pulsations after prior documented presence, however, suggests ICP elevation. Other ophthalmoscopic findings may include ONH and peripapillary cotton-wool spots, exudates, and hemorrhage.

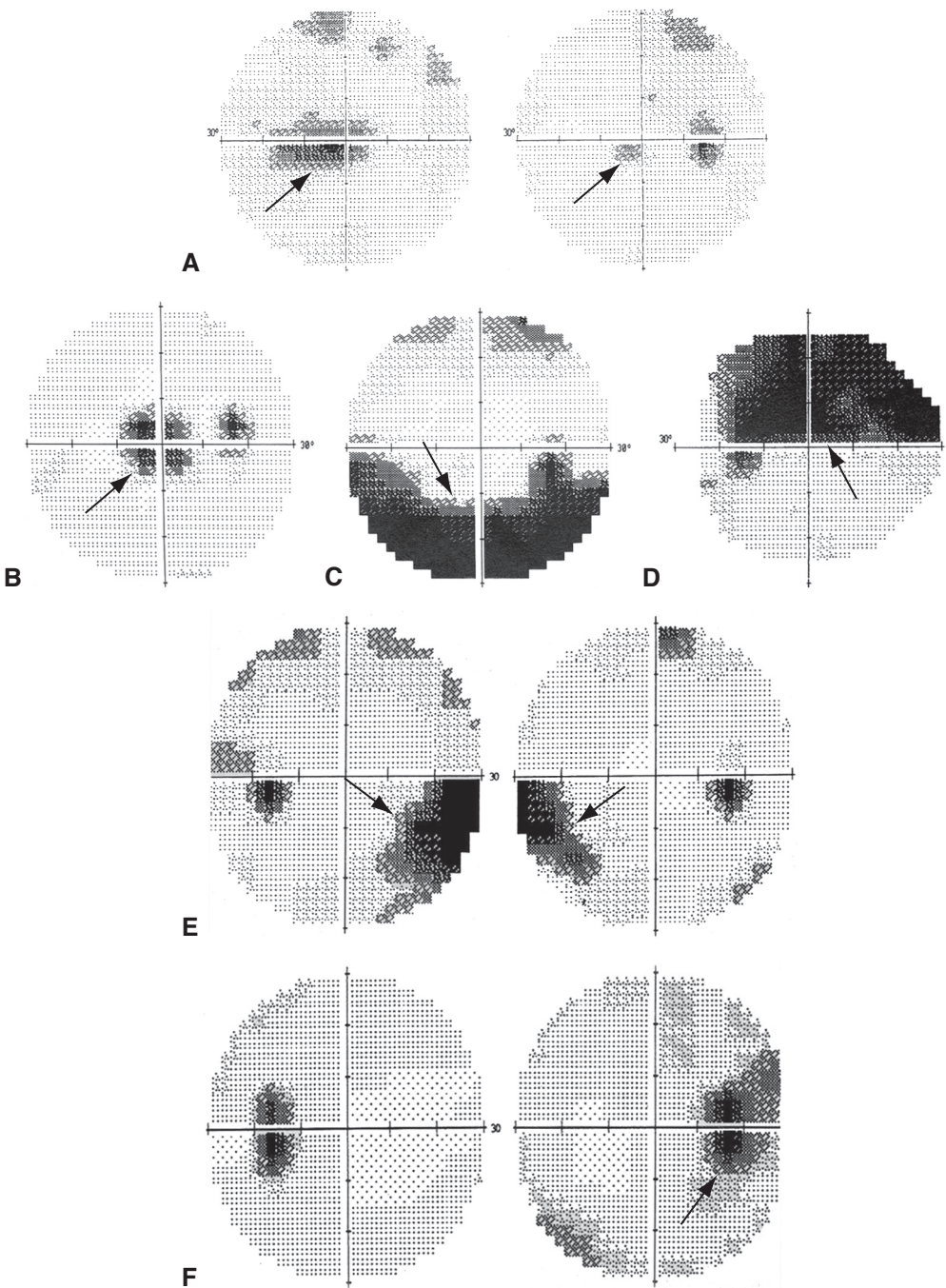


Figure 4-3 Patterns of visual field loss in optic neuropathies, as shown on automated perimetry. **A**, Cecocentral scotoma in the left eye (left; arrow); paracentral scotoma in the right eye (right; arrow). **B**, Central scotoma in the right eye (arrow). **C**, Arcuate scotoma in the right eye (arrow). **D**, Broad arcuate (altitudinal) defect in the left eye (arrow). **E**, Nasal arcuate (step) defects in both eyes (arrows). **F**, Enlarged blind spot in the right eye (arrow), worse than in the left eye. (Parts E, F courtesy of Anthony C. Arnold, MD.)

Table 4-3 Mechanisms of Optic Neuropathies

Papilledema (raised intracranial pressure)
Glaucoma
Inflammatory (optic neuritis)
Idiopathic optic neuritis (associated with MS)
Neuromyelitis optica (Devic disease)
Infections
Systemic inflammatory disorders
Vascular (ischemic optic neuropathy)
Anterior/posterior
Arteritic/nonarteritic
Compressive/infiltrative
Neoplastic
Nonneoplastic
Hereditary
Toxic/nutritional
Traumatic
Anomalous optic nerve
Congenitally anomalous
Drusen

MS = multiple sclerosis.

Most patients with elevated ICP report symptoms such as headache, nausea, and vomiting. Patients may also note transient visual obscurations—episodes of unilateral or bilateral vision loss lasting seconds. These episodes are described as “grayouts,” “whiteouts,” or “black-outs” of vision, often occurring with orthostatic changes. In patients with idiopathic intracranial hypertension (IIH), these obscurations are not prognostic of optic nerve damage.

In early papilledema, optic nerve function, including visual acuity and color vision, is usually normal. Pupillary responses are also normal; visual fields demonstrate only enlargement of the blind spot (see Fig 4-1).

The clinician’s first step in managing suspected papilledema is to rule out pseudopapilledema. The following fundusoscopic features suggest true ONH edema:

- hyperemia
- microvascular abnormalities on the ONH surface, such as telangiectasia or flame hemorrhages
- opacification of the peripapillary retinal RNFL

Most cases of pseudopapilledema result from ONH drusen (Fig 4-4; also see discussion later in this chapter).

An elevated ONH appearance mimicking papilledema may also be caused by hyaloid remnants and glial tissue on the ONH surface, congenital “fullness” of the ONH associated with entry of the optic nerve into the eye through a relatively small scleral canal, or ONH fullness associated with hyperopia. Vitreopapillary traction can cause a swollen-appearing ONH. Obscuration of ONH margins can occur without ONH elevation from myelination of the RNFL (Fig 4-5). Myelination typically occurs at the ONH margin, where it obscures

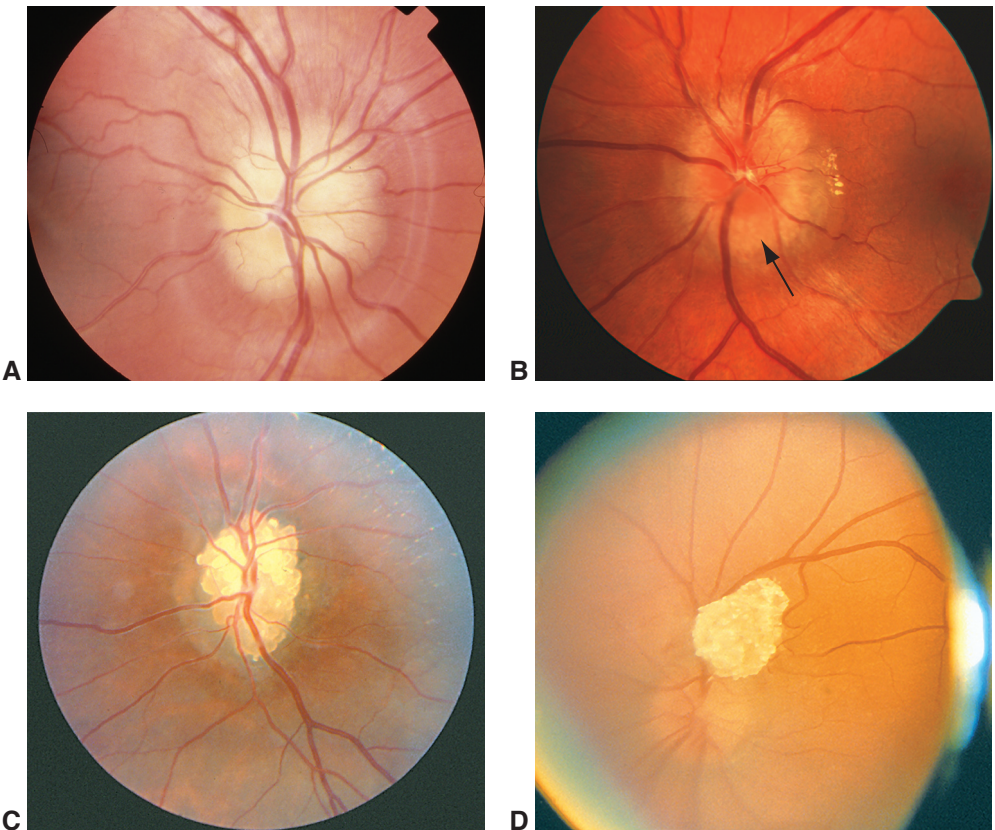
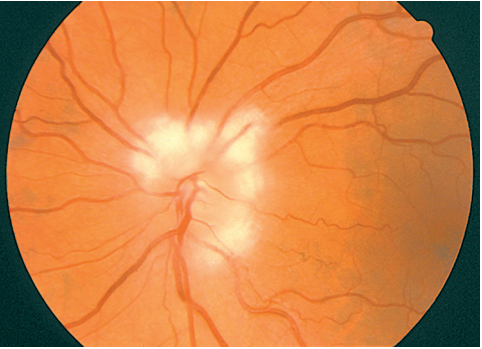


Figure 4-4 Appearance of optic disc drusen (ODD). **A**, Fundus photograph of the ONH with buried drusen. The ONH margin is blurred, with yellowish opacity of the deep peripapillary tissue. The retinal vessels are clearly visible overlying the ONH. **B**, Fundus photograph of the ONH with papilledema. The ONH margin is blurred, with grayish-white, opalescent thickening of the peripapillary nerve fiber layer (*arrow*). The retinal vessels are partially obscured at the ONH margin and within the peripapillary retina. There are exudates from chronic edema just temporal to the ONH. **C**, Surface drusen demonstrate prominent refractile nodules on the ONH surface, which do not obscure retinal vessels. **D**, Astrocytic hamartomas are nodular masses arising from peripapillary retina and obscure the retinal vessels. (*Parts A, B courtesy of Sophia M. Chung, MD; parts C, D reprinted from Arnold AC. Optic disc drusen. Ophthalmol Clin North Am. 1991;4:505–517.*)

Figure 4-5 Myelinated nerve patches are often present within the arcuate bundles, occasionally abutting the ONH. When they are contiguous, these nerve patches may be mistaken for ONH edema or cotton-wool spots. (*Courtesy of Anthony C. Arnold, MD.*)



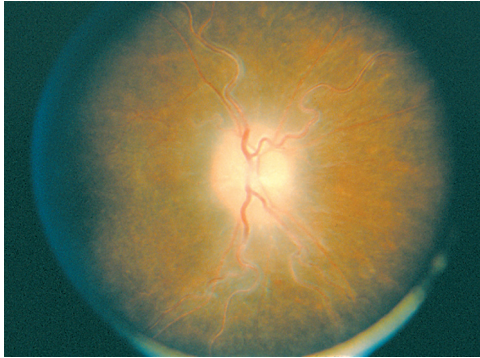


Figure 4-6 Chronic atrophic papilledema with gliosis and retinal vascular sheathing. (Courtesy of Anthony C. Arnold, MD.)

the ONH–retina border; myelination in the RNFL also obscures the retinal vessels and results in a feathered edge that resembles true edema. Myelination appears as a dense, white opacity compared with the partially translucent, grayish-white appearance of true edema. Papilledema may result from a variety of conditions, including

- an intracranial mass
- hydrocephalus
- meningeal processes, such as an infection of the central nervous system (CNS) or infiltration by a granulomatous or neoplastic process
- increased venous pressure from cerebral venous thrombosis or dural fistula
- IIH (discussed later in this chapter)

Suspicion of papilledema warrants urgent brain imaging, ideally MRI and magnetic resonance venography (MRV) of the brain and orbits with contrast, to rule out an intracranial mass lesion and cerebral venous thrombosis. Normal brain imaging results should prompt evaluation of the cerebrospinal fluid (CSF) opening pressure and composition by lumbar puncture.

Katz BJ. The anomalous optic nerve. *Focal Points: Clinical Modules for Ophthalmologists*. San Francisco: American Academy of Ophthalmology; 2011, module 3.

Chronic papilledema Optic nerve function may deteriorate in patients with chronically (lasting months to years) elevated ICP and long-standing papilledema. The ONH may no longer appear hyperemic but may rather look pale as the result of chronic axonal loss (Fig 4-6). Additional features may include the following:

- *Gliosis of the peripapillary RNFL*. The opacification appears grayish, less “fluffy,” and more membranous than with edema. Gliosis tends to follow retinal vessels, producing vascular sheathing.
- *Optociliary shunt vessels (retinochoroidal collaterals)*, which are preexisting venous channels on the ONH surface that dilate in response to chronic central retinal vein obstruction from elevated ICP. Unlike congenital ONH anomalies or the retinal vascular anomalies often accompanying drusen, these collateral vessels follow an evolving course of enlargement over time and characteristically penetrate deep into the choroid immediately adjacent to the ONH.

- *Refractile bodies of the ONH*, which are the result of chronic lipid-rich exudation (Fig 4-7). Unlike drusen, these bodies tend to be smaller and noncalcified. They remain on the ONH surface rather than within its substance, with frequent clustering at the ONH margin, and disappear as papilledema resolves.

With chronic papilledema, visual field defects may include nasal field loss, arcuate scotomata, and generalized peripheral depression. Central visual field involvement with decreased visual acuity typically does not occur until late. The process is usually bilateral, but if asymmetric, an RAPD may occur.

Arnold AC. Differential diagnosis of optic disc edema. *Focal Points: Clinical Modules for Ophthalmologists*. San Francisco: American Academy of Ophthalmology; 1999, module 2.

Idiopathic intracranial hypertension Patients with IIH, also known as *pseudotumor cerebri*, present with symptoms and signs of elevated ICP. Headache is common. Other symptoms may include neck and back pain, transient visual obscurations, diplopia (secondary to abducens nerve paresis), pulsatile tinnitus (pulse synchronous bruit), and nausea. Almost all patients with IIH have papilledema. Neurologic abnormalities other

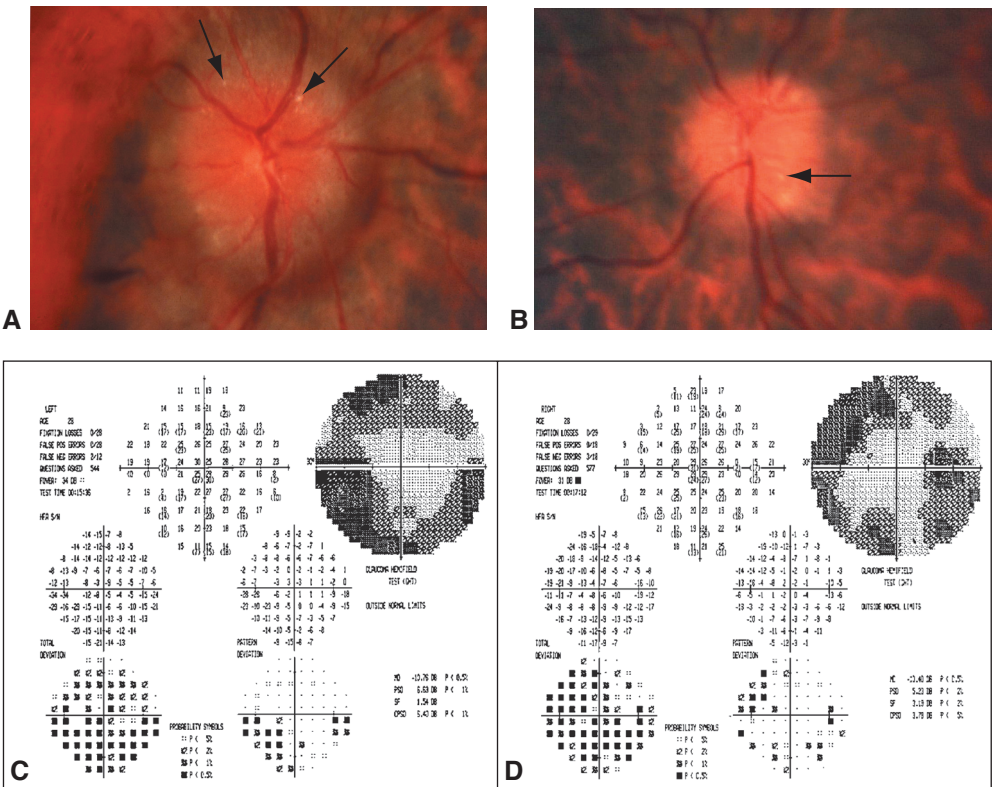


Figure 4-7 Chronic papilledema. **A, B**, ONHs in chronic papilledema, with the development of refractile bodies (arrows) representing lipid exudates from chronic microvascular leakage. **C, D**, Visual field patterns confirm the presence of mild diffuse depression in sensitivity and superior and inferior arcuate defects. (Parts A, B courtesy of Anthony C. Arnold, MD; parts C, D courtesy of Steven A. Newman, MD.)

than cranial nerve (CN) VI palsy are not associated with IIH. As with acute papilledema, early IIH shows normal visual acuity and enlarged blind spots on perimetry testing. Optic nerve function may deteriorate in long-standing, untreated, or severe cases.

The incidence of IIH peaks in the third decade of life. Ninety percent of patients are women, and 90% are obese. The disease is rare in prepubertal children (in whom obesity is less of a factor), men, and lean adults. Intracranial hypertension is associated with the use of exogenous substances such as vitamin A (>100,000 IU/day), tetracycline, minocycline, doxycycline, retinoic acid, and lithium, as well as the use of or withdrawal of use of corticosteroids. Sleep apnea may be associated with IIH. Although hormonal changes occurring during pregnancy and hormonal abnormalities have been implicated, IIH has not been definitively associated with any specific endocrinologic dysfunction. The reason for the increase in ICP in IIH remains obscure.

Cerebral venous disorders, such as cerebral venous thrombosis (resulting from trauma, childbirth, a hypercoagulable state, compression, or an ear or CNS infection), systemic or localized extracranial venous obstruction (eg, after radical neck dissection), a dural arteriovenous malformation, or systemic vasculitis, may lead to decreased venous outflow and thus increased ICP. Such conditions may resemble IIH, so patients with suspected IIH should undergo both neuroimaging with MRI to rule out a mass, hydrocephalus, or meningeal lesion and MRV to assess for venous sinus occlusion (see Chapter 2, Fig 2-13). Characteristic (but not specific) MRI findings of intracranial hypertension include flattening of the globes, enlarged optic nerve sheaths, partially empty sella, and narrowing of the distal transverse venous sinus. The clinician should always perform a lumbar puncture to confirm elevated ICP and to rule out infectious or inflammatory processes. Table 4-4 lists the diagnostic criteria of IIH.

The ophthalmologist plays a crucial role in the management of IIH. Careful long-term follow-up is essential to ensure that papilledema resolves and that vision remains normal. Regularly scheduled examinations should include testing of visual acuity, color vision, and quantitative perimetry to document the level of optic nerve function. Photographs of the ONH are essential to obtain during patient follow-up. Repeat OCT can also be used to document improvement of papilledema; however, OCT cannot be used in isolation to follow papilledema, because secondary optic atrophy from untreated papilledema

Table 4-4 Criteria for the Diagnosis of Idiopathic Intracranial Hypertension

Symptoms of increased ICP, such as headaches, neck pain, nausea, tinnitus, transient visual obscurations, or diplopia; no focal neurologic symptoms
Signs of isolated increased ICP, such as papilledema, unilateral or bilateral abducens nerve palsy, or divergence insufficiency
No evidence of ventriculomegaly or of mass, structural, or vascular lesions on brain imaging (ideally, MRI scan with contrast or CECT scan, associated with magnetic resonance venography or CT venography if presentation is atypical)
Documented elevated ICP, typically ≥ 25 cm H ₂ O in adults during lumbar puncture measured in the lateral decubitus position (≥ 28 cm H ₂ O in children)
Normal CSF composition

CECT = contrast-enhanced computed tomography; CSF = cerebrospinal fluid; CT = computed tomography; ICP = intracranial pressure; MRI = magnetic resonance imaging.

will also result in apparent improvement of the RNFL thickness on OCT. The ganglion cell complex at the macula may be helpful in differentiating a decrease in RNFL thickness due to optic atrophy (in which the ganglion cell complex will also show thinning) from that due to resolution of papilledema (in which the ganglion cell complex will remain normal). The frequency of visual field testing depends on the severity of papilledema, the level of optic nerve dysfunction, and the patient's response to treatment.

Treatment for IIH depends on symptomatology and vision status. The disease may be self-limited. If headache is mild or absent and optic nerve function is normal, no medical therapy may be required. However, untreated papilledema may result in severe vision loss in 5%–10% of patients with IIH. Poor visual prognosis is associated with male gender, African American race, morbid obesity, severe papilledema, and anemia. Patients with a fulminant course, with abnormal visual field testing at presentation, or with an RAPD (suggesting asymmetric damage to the optic nerve from severe papilledema) are also at high risk of permanent vision loss.

For patients with obesity, weight loss can be an effective treatment and is always recommended; moderate weight loss alone can lead to resolution of the signs and symptoms of IIH. Referral to a nutritionist is helpful, and in some cases, bariatric surgery might be considered.

For patients requiring medical therapy, acetazolamide is usually the first choice. In 2014, a large randomized clinical trial, the Idiopathic Intracranial Hypertension Treatment Trial, showed that acetazolamide (1–4 g/day) in association with weight loss was effective in reducing ICP and improved papilledema in patients who had IIH and moderate visual field defects. Topiramate may also be helpful for such patients, especially those with chronic headaches. Topiramate has multiple beneficial effects, including headache control, appetite suppression, and carbonic anhydrase inhibition. Furosemide may also be used in patients who cannot tolerate acetazolamide or topiramate. Corticosteroids should be avoided; although ICP can improve with use of corticosteroids, recurrence commonly occurs during corticosteroid taper, and these drugs may result in weight gain with subsequent worsening of IIH. However, a short course of high-dose intravenous corticosteroids may benefit patients presenting with severe papilledema and vision loss (fulminant IIH). Repeat lumbar punctures are not recommended therapy for patients with IIH.

In cases of progressive vision loss despite maximally tolerated medical therapy, surgical therapy is recommended. In some patients with severe vision loss and papilledema, surgical intervention may be considered without waiting for definite evidence of progression. The primary surgical options are optic nerve sheath fenestration (ONSF) or a CSF diversion procedure (lumboperitoneal or ventriculoperitoneal shunt).

For patients with substantial loss of vision without prominent headache, ONSF is often the preferred surgical option because it directly protects the optic nerve and has lower morbidity than that associated with shunting. However, ONSF carries an overall risk of complication of approximately 10%–15%, including a 1%–2% risk of vision loss from optic nerve injury, central retinal artery occlusion (CRAO), or central retinal vein occlusion (CRVO). ONSF does not significantly lower ICP and thus often does not reliably treat headache. Papilledema in the contralateral eye might be reduced, but bilateral ONSF may be required. The long-term success rate of ONSF remains unclear. Repeat ONSF procedures may be performed but are technically more difficult because of scarring.

Lumboperitoneal or ventriculoperitoneal shunting procedures effectively lower ICP, leading to improvement of headache, CN VI palsy (if present), and papilledema. Moreover, shunting entails no direct risk to the optic nerve. A shunt, however, may become occluded, infected, or altered in position, requiring reoperation in many cases.

Endovascular stenting of a stenosed venous transverse sinus can also decrease CSF pressure and may improve headaches and papilledema. However, this procedure remains controversial and should be performed only in specialized centers.

Many patients with IIH have chronic headaches despite effective treatment of increased ICP and improvement of papilledema. Usually these headaches are not directly related to increased ICP, and they should be managed medically with the help of a neurologist.

IIH also occurs in children. It appears to be a different disorder in prepubertal children, as there is no gender predilection and more children without obesity are affected. Recent studies have shown that normal CSF opening pressure among children is higher than previously believed and may be as high as 28 cm H₂O. The treatment for pediatric IIH is similar to that for adult IIH.

Bidot S, Bruce BB. Update on the diagnosis and treatment of idiopathic intracranial hypertension. *Semin Neurol.* 2015;35(5):527–538.

Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology.* 2013;81(13):1159–1165.

Markey KA, Mollan SP, Jensen RH, Sinclair AJ. Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions. *Lancet Neurol.* 2016;15(1):78–91.

Wall M, McDermott MP, Kieburtz KD, et al; NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. *JAMA.* 2014;311(16):1641–1651.

Optic neuritis

The term *optic neuritis* refers to any cause of optic nerve inflammation. It may be isolated or related either to a neurologic inflammatory or infectious disorder or to a local or systemic inflammatory disease. It may affect any portion of the nerve. When it affects the posterior portion of the optic nerve, the ONH appears normal at the time of vision loss (*retrobulbar optic neuritis*); when the inflammation involves the anterior portion of the nerve, the ONH appears edematous, a condition that is sometimes called *papillitis*. The ONH edema is usually hyperemic and diffuse. Papillitis is more common in postviral and infectious neuritis than in demyelinating neuritis, but considerable overlap exists. Children, in particular, manifest postviral optic neuritis and papillitis, which typically presents with profound bilateral vision loss.

Beck RW, Trobe JD, Moke PS, et al; Optic Neuritis Study Group. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. *Arch Ophthalmol.* 2003;121(7):944–949.

Optic Neuritis Study Group. Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up. *Arch Neurol.* 2008;65(6):727–732.

Isolated optic neuritis Isolated optic neuritis typically occurs in young (mean age, 32 years) female (77%) patients, and it presents as subacute monocular vision loss that develops over several days. Periorbital pain, particularly with eye movement, occurs in

92% of cases and often precedes vision loss. The retrobulbar form occurs in 65% of cases, and only one-third of patients have ONH edema. Unless the optic neuritis is bilateral and symmetric, an RAPD is also present. Perimetry testing most often shows a central depression or generalized reduction of sensitivity (48%), but any pattern of visual field loss may appear (Fig 4-8). Dyschromatopsia, particularly for red-green, is nearly universal and is often out of proportion to the loss of visual acuity. In the vast majority of cases, optic neuritis shows spontaneous improvement within 1 month.

Most cases of optic neuritis are either isolated (eg, clinically isolated syndrome [CIS]) or are part of a demyelinating disorder (eg, multiple sclerosis [MS]). Atypical features that should prompt further evaluation for alternative etiologies include older age, lack of pain, persistent pain or vision loss, significant swelling of the ONH with peripapillary

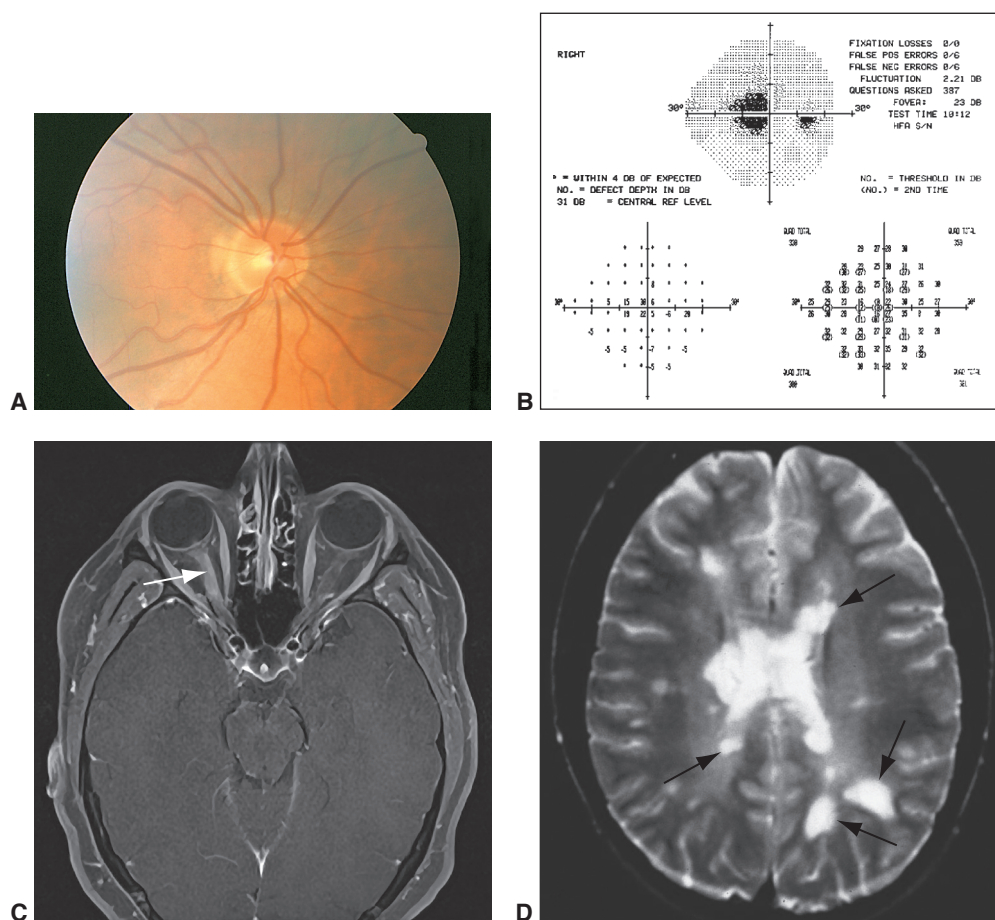


Figure 4-8 Isolated optic neuritis. **A**, ONH photograph of acute retrobulbar optic neuritis, showing normal appearance. **B**, Automated perimetry shows a central scotoma in the right eye. **C**, T1-weighted axial magnetic resonance imaging (MRI) scan of the orbits with fat suppression and gadolinium administration, showing enhancement of the right intraorbital optic nerve (arrow). **D**, T2-weighted axial MRI scan of the brain, demonstrating multiple white matter hyperintensities (arrows) consistent with demyelination. (Parts A, B courtesy of Steven A. Newman, MD; part C courtesy of Michael S. Lee, MD; part D courtesy of Anthony C. Arnold, MD.)

hemorrhages or exudates, inflammatory ocular features (eg, uveitis, phlebitis, choroiditis, pars planitis), retinal changes, bilateral vision loss, involvement of other CNs, steroid-responsive optic neuropathy, and lack of any vision recovery by 1 month. Additional hematologic, serologic, or other testing may be of value in atypical cases but need not be performed routinely. Such studies may include the following:

- serum and CSF rapid plasma reagin and fluorescent treponemal antibody absorption testing for syphilis
- serum testing for *Bartonella* infection
- serum testing for Lyme disease (if endemic)
- chest x-ray or chest computed tomography (CT), gallium scan or full-body positron emission tomography (PET), serum angiotensin-converting enzyme testing for sarcoidosis
- erythrocyte sedimentation rate (ESR) determination, antinuclear antibody testing, and anti-DNA antibody testing for systemic lupus erythematosus or vasculitis
- antineutrophil cytoplasmic antibodies (ANCA) for granulomatosis with polyangiitis (Wegener granulomatosis)
- serum or CSF aquaporin-4 immunoglobulin G (AQP4-IgG) antibody testing and spinal MRI for neuromyelitis optica spectrum disorder (NMOSD) (see later in this chapter)
- genetic testing for Leber hereditary optic neuropathy (LHON)
- brain and orbit MRI with gadolinium contrast for compressive, infiltrative disorders
- lumbar puncture with cytology for a meningeal process

Several studies have clarified the natural history of isolated optic neuritis. The Optic Neuritis Treatment Trial (ONTT) 10-year follow-up study reported that optic neuritis recurred in the affected or fellow eye in 35% of cases overall and in 48% of patients with conversion to MS. Most eyes with a recurrence regained normal or almost-normal vision. After 15 years of follow-up in the ONTT, 92% of patients with optic neuritis recovered visual acuity of 20/40 or better; 3% had final visual acuities of 20/200 or worse. Despite their seemingly excellent prognosis, patients with optic neuritis usually remain aware of visual deficits in the affected eye after recovery. Studies using measures of visual function other than Snellen visual acuity (ie, color vision, contrast sensitivity, motion detection, stereopsis, perimetry) show residual abnormalities in up to 90% of patients with visual acuities of at least 20/30.

In the absence of a known diagnosis of MS, MRI of the brain should be performed in every case of optic neuritis. Evaluation for periventricular white-matter lesions consistent with demyelination is the best way to assess the risk of future MS in patients with isolated optic neuritis and to guide subsequent decisions on the use of immunomodulation therapy (see the following section). The 15-year data from the ONTT found a risk for MS of 25% for patients with no lesions on MRI versus 72% for patients with at least 1 lesion, with the highest rate of conversion within the first 5 years. Patients with normal MRI results and no conversion to MS by year 10 had only a 2% risk of conversion by year 15 (see Chapter 14). Among patients with normal baseline MRI results, a lower risk of future MS was associated with male sex, ONH swelling, and atypical features of optic neuritis (absence of pain, no light perception vision, peripapillary hemorrhages, and retinal exudates).

Treatment of optic neuritis The ONTT demonstrated that corticosteroid therapy for optic neuritis had no long-term beneficial effect on vision, although the use of intravenous methylprednisolone, 250 mg every 6 hours for 3 days, followed by oral prednisone, 1 mg/kg/day for 11 days (with a quick taper of 4 days), sped recovery by 1–2 weeks. Patients receiving oral prednisone alone experienced no improvement in vision, and their recurrence rate was twice as high as that of the other groups. Therefore, oral prednisone (1 mg/kg/day) is not recommended for the treatment of isolated optic neuritis. The use of high-dose intravenous corticosteroids reduced the rate of development of clinically definite MS after the initial optic neuritis only in the subgroup of patients with MRI scans showing 2 or more white matter lesions. At 2 years, the risk of MS was 36% for the untreated group versus 16% for the treated group. However, by follow-up year 3 and thereafter, this “protective” effect was lost.

Given that the benefits are uncertain, the value of therapy and of additional diagnostic evaluation for MS must be assessed for each individual patient. In cases in which a rapid return of vision is essential (eg, in monocular patients or patients with an occupational need), intravenous methylprednisolone may be considered. The main purpose of the MRI scan is to assess the future risk of MS, but additional evaluation, including CSF analysis, is probably best referred to a consulting neurologist.

Immunomodulatory therapy is of proven benefit for reducing morbidity in the relapsing-remitting form of MS, and studies have shown that such drugs can delay conversion to MS in patients with acute optic neuritis or another CIS associated with an abnormal MRI (see Chapter 14 for a discussion of MS treatment).

Beck RW, Cleary PA, Anderson MM Jr, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. *N Engl J Med*. 1992;326(9):581–588.

Galetta SL, Villoslada P, Levin N, et al. Acute optic neuritis: unmet clinical needs and model for new therapies. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(4):e135. <http://nn.neurology.org/content/2/4/e135>. Published July 23, 2015. Accessed January 31, 2017.

Optic Neuritis Study Group. Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up. *Arch Neurol*. 2008;65(6):727–732.

Optic Neuritis Study Group. Visual function 15 years after optic neuritis: a final follow-up report from the Optic Neuritis Treatment Trial. *Ophthalmology*. 2008;115(6):1079–1082.

Chronic relapsing inflammatory optic neuropathy Chronic relapsing inflammatory optic neuropathy (CRION) is an isolated inflammatory optic neuritis that is very steroid responsive and steroid dependent. It usually occurs chronically over months or years and requires long-term corticosteroid and/or immunosuppressive therapy. CRION is not associated with MS. In cases of suspected CRION, other inflammatory disorders such as sarcoidosis must be ruled out.

Petzold A, Plant GT. Chronic relapsing inflammatory optic neuropathy: a systematic review of 122 cases reported. *J Neurol*. 2014;261(1):17–26.

Neuromyelitis optica Optic neuritis and acute myelitis characterize neuromyelitis optica (NMO), also known as Devic disease. NMOSD denotes a first attack or limited form of optic neuritis or transverse myelitis, as well as typical clinical NMO associated with cerebral, diencephalic, or brainstem lesions. Table 4-5 presents a set of diagnostic criteria for

Table 4-5 Criteria for the Diagnosis of NMOSD in Adult Patients

Core Clinical Characteristics	Diagnostic Criteria for NMOSD With AQP4-IgG	Diagnostic Criteria for NMOSD Without AQP4-IgG or NMOSD With Unknown AQP4-IgG Status	Additional MRI Requirements for NMOSD Without AQP4-IgG and NMOSD With Unknown AQP4-IgG Status
- Optic neuritis - Acute myelitis - Area postrema syndrome: episode of otherwise-unexplained hiccups or nausea and vomiting - Acute brainstem syndrome - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions - Symptomatic cerebral syndrome with NMOSD-typical brain lesions	- At least 1 core clinical characteristic - Positive test for AQP4-IgG - Exclusion of alternative diagnoses	- At least 2 core clinical characteristics occurring as a result of 1 or more clinical attacks and meeting all of the following requirements: - At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome - Dissemination in space (2 or more different core clinical characteristics) - Fulfillment of additional MRI requirements, as applicable - Negative tests for AQP4-IgG - Exclusion of alternative diagnoses	- Acute optic neuritis: a brain MRI showing normal findings (or only nonspecific white matter lesions), or an optic nerve MRI with a T2-hyperintense lesion or a T1-weighted gadolinium-enhanced lesion extending over more than one-half the optic nerve length or involving the optic chiasm - Acute myelitis: an associated intramedullary MRI lesion extending over either ≥ 3 contiguous segments (LETM) or ≥ 3 contiguous segments of focal spinal cord atrophy in patients with a history compatible with acute myelitis - Area postrema syndrome: associated dorsal medulla/area postrema lesions - Acute brainstem syndrome: associated peripendymal brainstem lesions

AQP4 = aquaporin-4; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis lesions; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorder.

Adapted from Wingerchuk DM, Banwell B, Bennett JL, et al; International Panel for NMO Diagnosis. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177–189.

NMOSD developed by an international group of experts. These criteria provide 99% sensitivity and 90% specificity. The AQP4-IgG test alone has 76% sensitivity and 94% specificity.

Although many patients experience myelitis and optic neuritis within weeks to months of each other, the episodes may be separated by several years. The vision and neurologic prognoses in NMO are poorer than in MS. The episodes of vision loss tend to recur; severe vision impairment (<20/200) is common in at least 1 eye. Testing for AQP4-IgG should be considered for patients with optic neuritis in the following scenarios:

- profound vision loss
- irreversible vision loss (lack of vision improvement by 1 month)
- bilateral optic neuritis
- recurrent optic neuritis
- extensive enhancement of the optic nerve on MRI

The mainstay of treatment during the acute period remains high-dose intravenous corticosteroids. For poorly responsive NMO, administration of plasmapheresis or intravenous immunoglobulin, in addition to high-dose intravenous methylprednisolone, may be considered. Use of other immunosuppressive drugs such as azathioprine or rituximab can reduce the risk of relapse.

Papais-Alvarenga RM, Carellos SC, Alvarenga MP, Holander C, Bichara RP, Thuler LC. Clinical course of optic neuritis in patients with relapsing neuromyelitis optica. *Arch Ophthalmol.* 2008;126(1):12–16.

Wingerchuk DM, Banwell B, Bennett JL, et al; International Panel for NMO Diagnosis. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology.* 2015;85(2):177–189.

Neuroretinitis

Neuroretinitis is an inflammatory disorder characterized by acute loss of vision associated with ONH edema and a star pattern of exudates in the macula (Fig 4-9). Mild vitritis and choroidal lesions may also occur. The diffuse ONH edema spreads through the

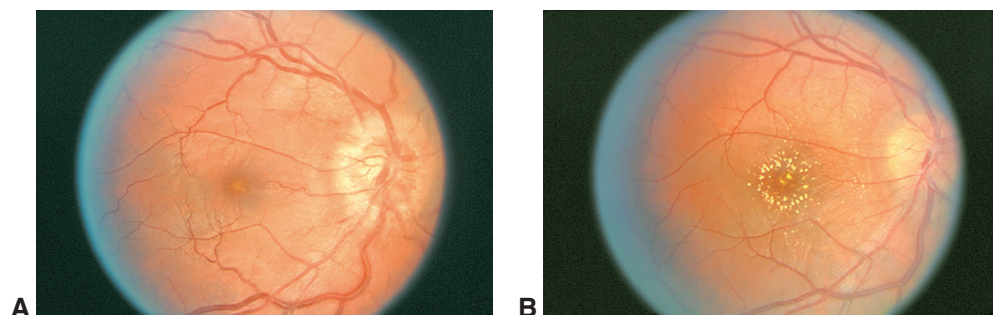


Figure 4-9 A 23-year-old man with a 2-day history of blurred vision on the right (visual acuity: 20/40 OD, 20/20 OS). **A**, The ONH on the right side is elevated and hyperemic, with obscuration of the nerve fiber layer. **B**, Five weeks after onset, funduscopic examination shows a macular star, characteristic of neuroretinitis. ONH edema is now less prominent. (Courtesy of Steven A. Newman, MD.)

outer plexiform layer along the papillomacular bundle and around the fovea. As the fluid resorbs, the lipid precipitates in a characteristic radial pattern in the Henle layer. The macular star can appear at initial presentation or several days later. Recognizing fluid or lipid exudates in the papillomacular bundle is crucial for establishing the correct diagnosis and differentiating neuroretinitis from optic neuritis, as patients with neuroretinitis do not have an increased risk of MS. Neuroretinitis is usually an infectious or postviral autoimmune process, frequently associated with elevated antibody immunoglobulin M (IgM) titers for *Bartonella quintana* or *Bartonella henselae*—the most common cause of neuroretinitis and cat-scratch disease. No definitive evidence exists that corticosteroids and antibiotics have a beneficial effect on visual outcome.

Other potential infectious and inflammatory causes of neuroretinitis include Lyme disease, sarcoidosis, syphilis, toxoplasmosis, tuberculosis, and viruses. See BCSC Section 9, *Uveitis and Ocular Inflammation*, for a complete discussion of ocular bartonellosis and neuroretinitis, as well as other possible causes.

Chi SL, Stinnett S, Eggenberger E, et al. Clinical characteristics in 53 patients with cat scratch optic neuropathy. *Ophthalmology*. 2012;119(1):183–187.

Optic perineuritis

Optic perineuritis is inflammation of the optic nerve sheath. Similarities between optic neuritis and optic perineuritis include acute, painful vision loss and a female predilection. However, patients are generally older (36% are older than 50 years), vision loss is often milder (central vision is relatively spared but with peripheral vision loss) and progresses over several weeks, and pain persists until treatment is initiated. Orbital MRI scans show enhancement of the optic nerve (dural) sheath rather than the optic nerve itself. Although the neuroimaging results can appear similar to those of optic nerve sheath meningioma, pain helps differentiate the 2 conditions. Distinguishing optic perineuritis from optic neuritis is important with respect to not only treatment, but also prognosis for the development of MS, as optic perineuritis is not associated with MS. Patients with optic perineuritis respond immediately and dramatically to corticosteroid treatment, but relapses are common with short courses of treatment. Without treatment, patients incur progressive loss of vision.

Purvin V, Kawasaki A, Jacobson DM. Optic perineuritis: clinical and radiographic features. *Arch Ophthalmol*. 2001;119(9):1299–1306.

Ischemic optic neuropathy

Ischemic optic neuropathy is classified as either anterior ischemic optic neuropathy (AION) or posterior ischemic optic neuropathy (PION), depending on which segment of the optic nerve is affected. AION accounts for 90% of all ischemic optic neuropathies.

Anterior ischemic optic neuropathy AION is the most common acute optic neuropathy in patients older than 50 years. Patients with AION experience painless monocular vision loss that develops over hours to days. Visual acuity may be relatively preserved, but visual field loss always occurs. Altitudinal and other variants of arcuate defects are typical, although any defect may occur. An RAPD is present unless the optic neuropathy becomes bilateral. By definition, there is always ONH edema at onset, which may precede the vision loss.

Table 4-6 Arteritic Versus Nonarteritic Anterior Ischemic Optic Neuropathy

Characteristic	Arteritic Features	Nonarteritic Features
Age	Mean, 70 years	Mean, 60 years
Sex	Affects more females than males	Affects males and females equally
Associated symptoms	Headache, scalp tenderness, jaw claudication, transient vision loss	Usually none
Visual acuity	<20/200 in >60% of cases	>20/200 in >60% of cases
ONH/fundus	Pallid ONH edema common Cup normal Cotton-wool spots Choroidal or retinal ischemia	Hyperemic ONH edema Cup small
ESR	Elevated	Normal
CRP	Elevated	Normal
Platelet count	Elevated or normal	Normal
Fluorescein angiography findings	ONH delay and choroid delay	ONH delay
Natural history	Condition rarely improves Fellow eye involved, 54%–95% within 1–2 weeks	31% of cases improve Fellow eye involved, 12%–19% at 5 years
Treatment	Systemic steroids	None proven

CRP = C-reactive protein level; ESR = erythrocyte sedimentation rate; ONH = optic nerve head.

AION is subclassified as either *arteritic anterior ischemic optic neuropathy* (AAION), in which case it is associated with vasculitis, most commonly giant cell arteritis (GCA), or *nonarteritic anterior ischemic optic neuropathy* (NAION) (Table 4-6). The most important initial step in evaluating AION is to distinguish between these two subtypes.

ARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY AAION is less frequent (5%–10% of AION cases) than NAION and occurs in patients older than 50 years (mean age, 70 years). It is caused by inflammatory and thrombotic occlusion of the short posterior ciliary arteries. Systemic symptoms of GCA are usually present, including headache, scalp tenderness, jaw claudication, malaise, anorexia, weight loss, and fever. However, up to 25% of patients with vision loss from GCA have no systemic symptoms (so-called occult GCA). Although ESR and C-reactive protein (CRP) levels are usually elevated in GCA, 1 or both of these tests may be normal, at least initially. Transient vision loss or transient diplopia preceding AION is very suggestive of GCA.

Vision loss is typically severe (visual acuity is <20/200 in >60% of patients), and a lack of light perception vision should prompt an aggressive evaluation for GCA. Fundusoscopic clues to a diagnosis of AAION over NAION include the following:

- chalky-white ONH edema (in NAION, the ONH is often hyperemic) (Fig 4-10)
- cotton-wool spots away from the ONH, which indicate concurrent retinal ischemia (cotton-wool spots on or adjacent to the ONH can be present in NAION)
- delayed choroidal filling on fluorescein angiographic studies (normally, the choroid fills completely within 3–5 seconds, before the retinal arteries do) (see Chapter 3, Fig 3-7)
- normal or large cup in the fellow eye (in NAION, a small cup–disc ratio is common)

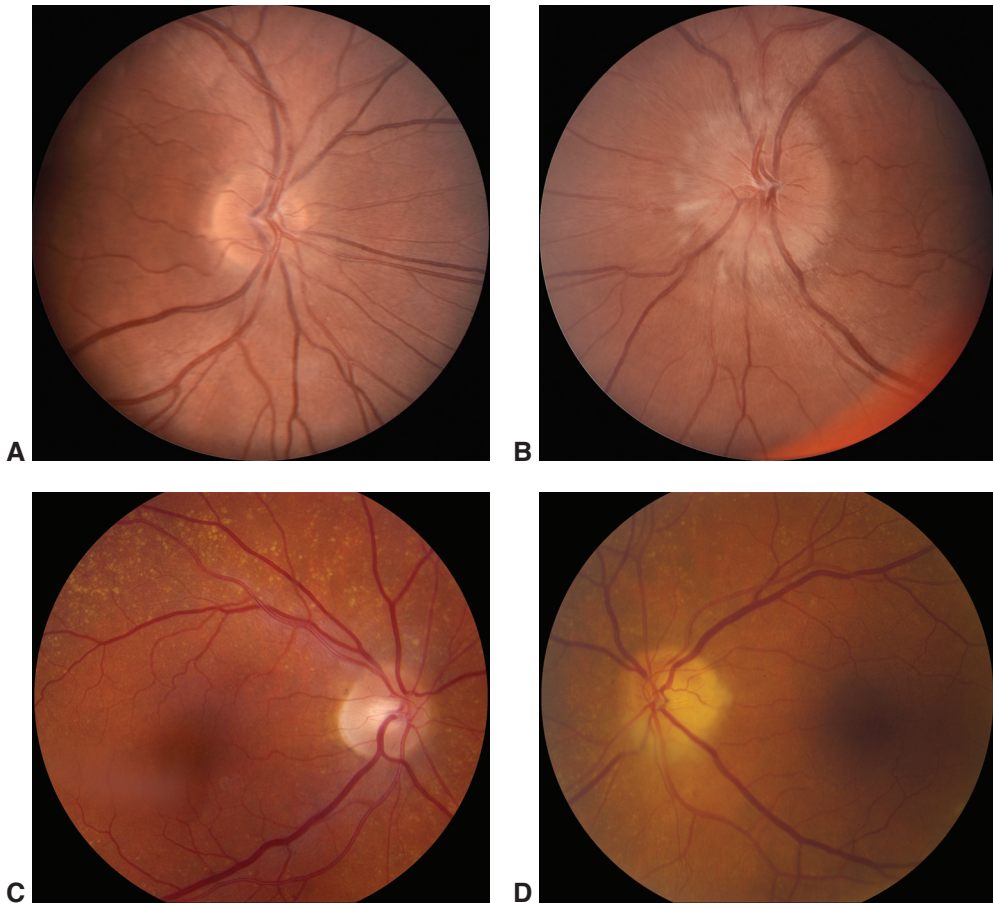


Figure 4-10 ONH appearance in nonarteritic anterior ischemic optic neuropathy (NAION) and arteritic anterior ischemic optic neuropathy (AAION). **A**, The healthy eye demonstrates a characteristic crowded appearance, which has been called “disc at risk.” **B**, ONH appearance in NAION. Edema is segmental, with mild superimposed pallor and flame hemorrhages. **C**, The healthy eye demonstrates a normal cup–disc ratio. Lack of a disc at risk should suggest an AAION. **D**, ONH appearance in AAION. Pallor is more pronounced. (Parts A, B courtesy of Michael S. Lee, MD; parts C, D courtesy of Rod Foroozan, MD.)

When AAION due to GCA is suspected, immediate initiation of high-dose corticosteroid therapy is crucial. Adjunctive daily aspirin can also be added. A temporal artery biopsy should be done to confirm the diagnosis as soon as possible, but it can be delayed for 1–2 weeks without compromising test results. Intravenous methylprednisolone (1 g/day for the first 3–5 days) is usually recommended. Thereafter, oral prednisone (1 mg/kg/day) may be used (up to 100 mg/day, tapered slowly over 12 months or more, depending on response).

The primary goal of AAION therapy (apart from avoiding systemic vascular complications) is to prevent contralateral vision loss. Untreated, the fellow eye becomes involved in up to 95% of cases, within days to weeks. Although the initially affected eye may improve somewhat, the patient’s vision does not fully recover. The risk of recurrent or contralateral optic nerve involvement during corticosteroid withdrawal has been reported at

7%. Therefore, tapering must be done slowly and carefully. Recurrent symptoms or elevation of ESR or CRP levels should prompt reevaluation for disease activity. For a discussion of the systemic effects, diagnostic evaluation, and treatment of GCA, see Chapter 14.

- Dasgupta B; Giant Cell Arteritis Guideline Development Group. Concise guidance: diagnosis and management of giant cell arteritis. *Clin Med (Lond)*. 2010;10(4):381–386.
- Hayreh SS, Bioussé V. Treatment of acute visual loss in giant cell arteritis: should we prescribe high-dose intravenous steroids or just oral steroids? *J Neuroophthalmol*. 2012;32(3):278–287.
- Lee AG, Brazis PW. Giant cell arteritis. *Focal Points: Clinical Modules for Ophthalmologists*. San Francisco: American Academy of Ophthalmology; 2005, module 6.
- Parikh M, Miller NR, Lee AG, et al. Prevalence of a normal C-reactive protein with an elevated erythrocyte sedimentation rate in biopsy-proven giant cell arteritis. *Ophthalmology*. 2006; 113(10):1842–1855.

NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY Compared with AAION, NAION is more common (accounting for 90%–95% of AION cases) and occurs in a relatively younger age group (mean age, 60 years), although it can occur at any age. The annual incidence is approximately 3.6–10.2 per 100,000. NAION is presumably related to compromised ONH microcirculation in eyes with structural “crowding” of the ONH. Histologic studies have shown that the area of infarction is located within the scleral canal alone, a finding supporting a potential local compartment syndrome. The initial course may remain *static*, in which case vision loss is stable from onset, or it may become *progressive*, which involves either episodic, stepwise decrements or a steady decline of vision over a few days to weeks before eventual stabilization. The progressive form occurs in approximately 12% of NAION cases and may be explained by the compartment syndrome theory. NAION is typically not associated with any systemic symptoms.

Vision loss is usually less severe in NAION (visual acuity >20/200 in >60% of cases) than in AAION. Visual acuity and color vision may be normal if fixation is spared but an RAPD is present. The most common pattern of visual field loss is an altitudinal defect, but any pattern may be observed. The ONH edema in NAION may be diffuse or segmental and is usually initially hyperemic (see Fig 4-10). The ONH in the contralateral eye is typically small in diameter and demonstrates a small or absent physiologic cup (“disc at risk”).

Within 6–8 weeks of NAION onset, the ONH usually becomes atrophic; persistence of edema past this point could suggest an alternative diagnosis. The 5-year risk of contralateral involvement is 15%. Occurrence in the second eye produces the clinical appearance of *pseudo-Foster-Kennedy syndrome*, in which the previously affected ONH is atrophic and the currently involved ONH is edematous. True Foster-Kennedy syndrome, by contrast, is secondary to intracranial mass and 1 ONH is atrophic because of chronic compression by the mass, whereas the other ONH is edematous because of elevated ICP.

NAION is associated with the following risk factors:

- structural crowding of the ONH (“disc at risk”)
- diabetes mellitus (particularly in young patients)
- systemic hypertension
- hyperlipidemia
- sleep apnea

Neither carotid occlusive disease nor a cardiac source of emboli are proven risk factors. Hypercoagulable disorders rarely cause NAION and should be investigated in young patients and patients with known thrombophilia or a family history of thrombosis. Nocturnal hypotension has been suggested as a precipitating factor, but this remains controversial. An association with phosphodiesterase 5-inhibitor (PDE5-inhibitor) drugs used primarily to treat erectile dysfunction has been suggested but remains debated. Amiodarone may trigger an anterior optic neuropathy with ONH edema similar to NAION.

NAION must be differentiated from optic neuritis, especially in younger patients (Table 4-7). In unclear cases, contrast-enhanced MRI of the orbits (with fat suppression) can help in the differentiation. The affected optic nerve appears normal in NAION (95% of cases) but enhanced in optic neuritis (90% of cases).

Untreated NAION generally remains stable after visual function has reached its low point, but the Ischemic Optic Neuropathy Decompression Trial (IONDT) showed that 43% of patients with a visual acuity worse than 20/64 at presentation regained at least 3 lines of visual acuity on the Snellen eye chart within 6 months. Recurrent episodes of vision loss in the same eye after 3 months are unusual in NAION (up to 6.4%), and should trigger a more extensive evaluation for an underlying systemic disorder or an alternative cause of the optic neuropathy.

There is no proven therapy for NAION. The IONDT showed that ONSF had no benefit for NAION; therefore, ONSF is no longer used to treat this condition. Treatment with steroids or neuroprotective drugs is not supported by any high-quality clinical studies.

There is also no proven prophylaxis for the fellow eye. Although aspirin is known to reduce the risk of secondary stroke, its role in reducing the incidence of fellow eye involvement after the initial episode remains unproven. Because at least 60% of NAION patients have systemic vascular risk factors, the clinician should look for and treat these factors when present. Although some studies recommend screening NAION patients for sleep apnea, there is no evidence that treating sleep apnea prevents second eye involvement.

Table 4-7 NAION Versus Optic Neuritis: Typical Features

	NAION	Optic Neuritis
Age	>50 years	<40 years
Associated pain	Unusual	With eye movement, 92%
Pupil	+ RAPD	+ RAPD
Visual field defect	Altitudinal	Central
ONH findings	Edema 100%	Edema 33%
Retinal hemorrhage	Common	Unusual
Fluorescein angiography findings	Delayed ONH filling	No delayed ONH filling
MRI findings	No optic nerve enhancement	Optic nerve enhancement

MRI = magnetic resonance imaging; NAION = nonarteritic anterior ischemic optic neuropathy; ONH = optic nerve head; RAPD = relative afferent pupillary defect.

Patients with NAION are at increased risk for cerebral ischemic stroke and therefore should be referred for risk factor modification and management.

- Arnold AC. Pathogenesis of nonarteritic anterior ischemic optic neuropathy. *J Neuroophthalmol.* 2003;23(2):157–163.
- Campbell UB, Walker AM, Gaffney M, et al. Acute nonarteritic anterior ischemic optic neuropathy and exposure to phosphodiesterase type 5 inhibitors. *J Sex Med.* 2015;12(1):139–151.
- Hayreh SS, Zimmerman MB. Non-arteritic anterior ischemic optic neuropathy: role of systemic corticosteroid therapy. *Graefes Arch Clin Exp Ophthalmol.* 2008;246(7):1029–1046.
- Lee MS, Grossman D, Arnold AC, Sloan FA. Incidence of nonarteritic anterior ischemic optic neuropathy: increased risk among diabetic patients. *Ophthalmology.* 2011;118(5):959–963.
- Lee YC, Wang JH, Huang TL, Tsai RK. Increased risk of stroke in patients with nonarteritic anterior ischemic optic neuropathy: a nationwide retrospective cohort study. *Am J Ophthalmol.* 2016;170:183–189.
- Newman NJ, Scherer R, Langenberg P, et al; Ischemic Optic Neuropathy Decompression Trial Research Group. The fellow eye in NAION: report from the ischemic optic neuropathy decompression trial follow-up study. *Am J Ophthalmol.* 2002;134(3):317–328.
- Pomeranz HD, Bhavsar AR. Nonarteritic ischemic optic neuropathy developing soon after use of sildenafil (viagra): a report of seven new cases. *J Neuroophthalmol.* 2005;25:9–13.
- Rizzo JF 3rd, Andreoli CM, Rabinov JD. Use of magnetic resonance imaging to differentiate optic neuritis and nonarteritic anterior ischemic optic neuropathy. *Ophthalmology.* 2002;109(9):1679–1684.

Posterior ischemic optic neuropathy Acute ischemic damage to the retrobulbar portion of the optic nerve is characterized by abrupt, often severe vision loss, an RAPD, and initially normal-appearing ONHs. PION is rare and is a diagnosis of exclusion. It occurs in 3 distinct scenarios: (1) perioperative (most commonly in spine, cardiac, and head or neck procedures); (2) arteritic (especially from GCA); and, in rare instances, (3) nonarteritic (with risk factors and a clinical course similar to those of NAION).

- Sadda SR, Nee M, Miller NR, Biousse V, Newman NJ, Kouzis A. Clinical spectrum of posterior ischemic optic neuropathy. *Am J Ophthalmol.* 2001;132(5):743–750.

Perioperative ischemic optic neuropathy Both AION and PION may be precipitated by various nonocular surgeries, often with profound and irreversible bilateral vision loss. The 2 most common procedures associated with ischemic optic neuropathies are coronary artery bypass grafting and prolonged spinal-fusion surgery with the patient in the prone position. Although the total reported incidence of this complication makes up no more than 0.3% of nonophthalmic surgeries, perioperative AION and PION have gained more widespread scrutiny because of the increasing number of reports and the potential medicolegal implications. AION occurs more frequently with cardiac surgery, whereas PION occurs more often with spine surgery. The causes of PION are poorly understood, and the contributing factors are probably multifactorial and different in these two procedures.

- Lee LA, Roth S, Posner KL, et al. The American Society of Anesthesiologists Postoperative Visual Loss Registry: analysis of 93 spine surgery cases with postoperative visual loss. *Anesthesiology.* 2006;105(4):652–659.

Lee MS, Armbrust KR. Perioperative visual loss in ocular and nonocular surgery. *Focal Points: Clinical Modules for Ophthalmologists*. San Francisco: American Academy of Ophthalmology; 2012, module 10.

Diabetic papillopathy

Diabetic papillopathy, which is related to NAION, can occur in patients with either type 1 or type 2 diabetes mellitus. Patients may have no symptoms or have nonspecific symptoms of blurred vision or “distortion” without pain. Evidence of optic nerve dysfunction (found via testing of visual acuity and visual field and for an RAPD) is variable. The optic nerve reveals hyperemic edema, but 50% of patients show marked dilation of the ONH surface microvasculature (Fig 4-11) that appears similar to neovascularization of the disc (NVD). However, the vessels in NVD proliferate into the vitreous cavity and leak fluorescein in angiographic studies. Diabetic retinopathy is not universal among patients with diabetic papillopathy (63%–80%); therefore, the absence of retinopathy does not preclude a diagnosis of diabetic papillopathy.

Untreated, the dilated, radially oriented vessels and ONH edema resolve slowly over 2–10 months. In rare cases, diabetic papillopathy progresses to vision loss (ie, AION). The pathophysiology is unclear but is suspected to be mild, reversible ischemia. Therefore, the distinction of diabetic papillopathy as an entity unique from AION remains controversial; the 2 disorders may instead represent a spectrum.

There is no proven therapy for diabetic papillopathy. Diabetes mellitus is discussed in BCSC Section 1, *Update on General Medicine*; associated ocular disorders are discussed in BCSC Section 12, *Retina and Vitreous*.

Bayraktar Z, Alacali N, Bayraktar S. Diabetic papillopathy in type II diabetic patients. *Retina*. 2002;22(6):752–758.

Regillo CD, Brown GC, Savino PJ, et al. Diabetic papillopathy. Patient characteristics and fundus findings. *Arch Ophthalmol*. 1995;113(7):889–895.

Papillophlebitis

Papillophlebitis, which represents a subset of CRVO, usually presents with vague blurring of vision or even transient visual obscurations. Visual acuity is typically normal or only mildly diminished. The pupils and color vision are normal, and visual field testing shows blind-spot enlargement. Fundus examination shows marked retinal venous engorgement associated with hyperemic ONH edema (Fig 4-12). Retinal hemorrhages extending to the equatorial region are common. Fluorescein angiographic studies typically show retinal



Figure 4-11 Fundus photograph of an ONH in diabetic papillopathy shows ONH edema with prominent surface telangiectasia. (Reprinted from Arnold AC. *Differential diagnosis of optic disc edema*. Focal Points: Clinical Modules for Ophthalmologists. San Francisco: American Academy of Ophthalmology; 1999, module 2.)

Figure 4-12 Fundus photograph shows papillophlebitis. ONH edema in a 28-year-old woman with engorgement and tortuosity of retinal venous system. Visual acuity is 20/30. (Reprinted from Kline LB, Foroozan R, eds. *Optic Nerve Disorders*. 2nd ed. *Ophthalmology Monographs* 10. New York: Oxford University Press, in cooperation with the American Academy of Ophthalmology; 2007:218.)



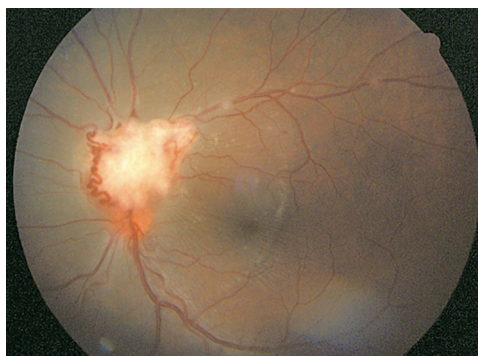
venous staining and leakage associated with circulatory slowing, without the regions of capillary occlusion observed in ischemic CRVO. An evaluation for hypercoagulable disorders should be considered. The condition usually resolves spontaneously over 6–12 months, with either no vision loss or only mild impairment related to incompletely resolved maculopathy. For further discussion on CRVO, see BCSC Section 12, *Retina and Vitreous*.

Compressive or infiltrative optic neuropathies

Patients with intraorbital or intracanalicular compressive lesions typically present with slowly progressive vision loss, an RAPD, and monocular visual field loss. There may be associated signs of orbital disease such as eyelid edema, eyelid retraction, lid lag, proptosis, ptosis, or ophthalmoplegia. The ONH may be normal or mildly atrophic at presentation, although anterior orbital lesions may produce ONH edema. Optociliary shunt vessels (also known as retinochoroidal collaterals) or choroidal folds may also be present.

The lesions that most commonly produce optic neuropathy include optic nerve sheath meningioma and optic nerve glioma. Cavernous hemangioma, although common in the orbit, only occasionally produces a compressive optic neuropathy. Infiltration (through inflammatory, infectious, or neoplastic mechanisms) of the optic nerve is usually a retrobulbar process, but anterior involvement may present with ONH edema. The ONH may simply be edematous or may display features of superimposed cellular infiltration. Visible prelaminar cellular infiltrate (diffuse or focal) tends to be more opaque, with a grayish or yellowish discoloration (Fig 4-13); the infiltrate may be denser and more opaque than in

Figure 4-13 Sarcoid optic neuropathy. Left fundus photograph of a 25-year-old man with a 1-month history of blurred vision. The patient's visual acuity was 20/50, and he had a moderate left afferent pupillary defect. The dense white elevation on the ONH represents granulomatous inflammation. A chest x-ray showed hilar adenopathy, and bronchoscopy confirmed sarcoidosis. (Courtesy of Steven A. Newman, MD.)



nonspecific edema. Focal granulomatous infiltration may consist of a focal nodule on the ONH surface. When edema and vision loss persist or progress in a way that is atypical for the common causes of optic neuropathy (eg, optic neuritis) or when prelaminar infiltrate is visible, ancillary testing for an infiltrative lesion should be performed.

If an orbital compressive lesion is suspected, neuroimaging is indicated. Although MRI of the orbits with contrast and fat suppression is best for evaluating soft-tissue abnormalities in the orbit, particularly in differentiating meningioma from glioma, a thin-section CT scan of the orbits with contrast remains a satisfactory option and is preferred for evaluation of calcification and bony abnormalities.

Optic nerve sheath meningioma and intracranial meningioma An optic nerve sheath meningioma (ONSM) arises from proliferations of the meningoepithelial cells lining the sheath of the intraorbital or intracanalicular optic nerve. Intracranial meningioma involving the optic nerve is the result of compression from the involved sphenoid wing or tuberculum sella (Fig 4-14; see also Chapter 2, Fig 2-7). Most meningiomas that involve the orbit represent extensions from intracranial sites, whereas true primary ONSMs are far less common and arise from the optic nerve sheath. Most ONSMs (95%) are unilateral.

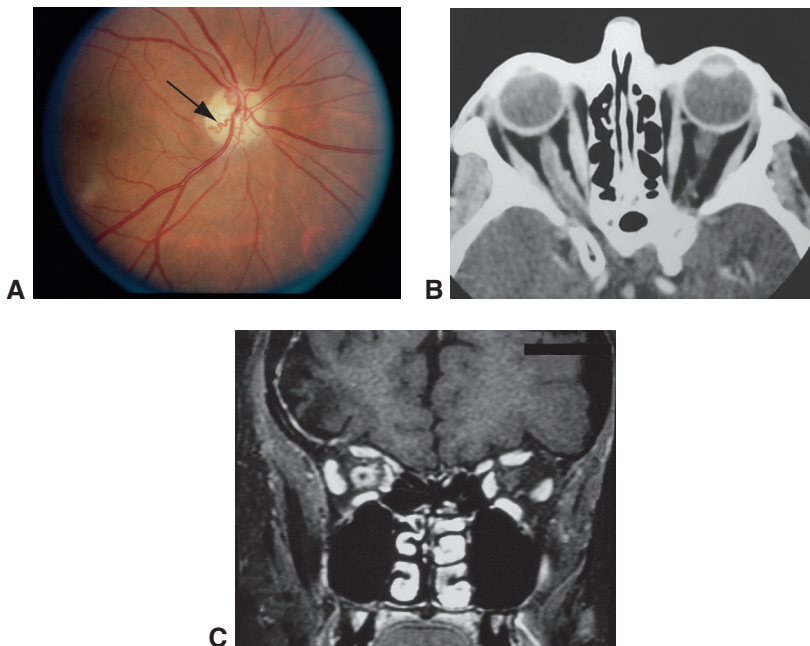


Figure 4-14 Optic nerve sheath meningioma. **A**, Fundus photograph shows ONH atrophy, with optociliary shunt vessels (retinochoroidal collaterals; arrow) visible at the 8- and 12-o'clock positions. **B**, Computed tomography (CT) scan reveals "tram track sign," diffuse enlargement of the right intraorbital optic nerve extending anteriorly to the globe, with enhancement of the optic nerve sheath. **C**, "Ring sign" in meningioma. Coronal orbital magnetic resonance imaging (MRI) scan shows similar optic nerve sheath enhancement surrounding a relatively normal, darker optic nerve on the right. (Parts A, C reprinted from Arnold AC. Optic nerve meningioma. Focal Points: Clinical Modules for Ophthalmologists. San Francisco: American Academy of Ophthalmology; 2004, module 7. Part B courtesy of Steven A. Newman, MD.)

Although ONSMs are uncommon (1%–2% of all meningiomas), they account for one-third of primary optic nerve tumors, second only to optic nerve glioma. They are usually detected in middle-aged women and are rare in children. Some patients may present with the classic diagnostic triad:

1. painless, slowly progressive monocular vision loss (see Chapter 2, Fig 2-16)
2. optic atrophy
3. optociliary shunt vessels

Optociliary shunt vessels or retinochoroidal collaterals are preexisting ONH channels that dilate in response to chronic obstruction of outflow through the central retinal vein. These vessels shunt retinal venous outflow to the choroidal circulation. They occur in approximately 30% of patients with ONSM but are nonspecific and can be seen in sphenoid wing meningioma, optic nerve glioma, CRVO, and chronic papilledema. Patients with ONSM also demonstrate an RAPD and an optic nerve–related visual field defect. Minimal to mild proptosis and mild ocular motility defects can also occur. ONH edema may be present, especially if the tumor extends anteriorly. Neuroimaging findings confirm the diagnosis (Table 4-8).

Fractionated radiation therapy is the treatment of choice for ONSM; it has been reported to produce stability or vision improvement in up to 95% of patients. However, it remains unclear whether radiation should be administered immediately upon diagnosis or when tumor growth or progressive vision loss is documented, because patients with ONSM may have minimal loss of vision for several years. In rare cases, radiation retinopathy and pituitary dysfunction have been reported as late radiation complications.

Surgery (ie, biopsy or excision) is typically ill-advised because of the considerable potential for significant vision loss. However, if the tumor extends intracranially or, in very

Table 4-8 Comparative Neuroradiologic Features Between Optic Nerve Sheath Meningioma and Optic Nerve Glioma

Optic Nerve Sheath Meningioma	Optic Nerve Glioma
Adjacent bony hyperostosis on CT scan	No calcification or hyperostosis on CT scan
Apical expansion of the tumor	Kinking or buckling of the optic nerve
Calcification of the nerve sheath on CT scan	Smooth sheath margins (no extradural extension)
Diffuse, tubular enlargement of the optic nerve	Fusiform or globular enlargement of the optic nerve
Extradural tumor extension	Regions of low intensity within the nerve (cystic spaces)
Isointense or mildly hyperintense to brain on T1- and T2-weighted MRI scan	Isointense or mildly hypointense to brain on T1-weighted MRI scan; hyperintense on T2-weighted MRI scan
Prominent contrast enhancement on CT and MRI scans	Variable-contrast (CT scan) and gadolinium (MRI scan) enhancement
Sheath thickening and enhancement, with relative sparing of optic nerve substance (“tram track” or “railroad track” signs)	Thickening of both nerve and sheath by tumor

CT = computed tomography; MRI = magnetic resonance imaging.

rare cases, across the planum sphenoidale, the risk of contralateral vision loss may warrant surgical debulking, particularly when severe ipsilateral vision loss is present. Radiation therapy is often performed following surgery on a residual tumor.

Observation is appropriate if there is no change in visual function or tumor size. ONSMs in children may be more aggressive, with more rapid vision loss and more frequent recurrence after therapy. Therefore, children must be monitored more frequently.

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Optic pathway glioma Although optic pathway gliomas (OPGs; also known as pilocytic astrocytomas) are generally uncommon (accounting for only about 1% of intracranial tumors), they are the most common primary tumor of the optic nerve. They may involve the optic nerve, the chiasm, or both (Fig 4-15).

Approximately 70% of OPGs are detected during the first decade of life and 90% by the second; however, they may occur at any age. There is no definite sex predilection. The most common presenting findings are proptosis (94%), vision loss (87.5%), ONH pallor (59%), ONH edema (35%), and strabismus (27%). Patients infrequently present with asymptomatic isolated optic atrophy. An RAPD is usually present in unilateral or

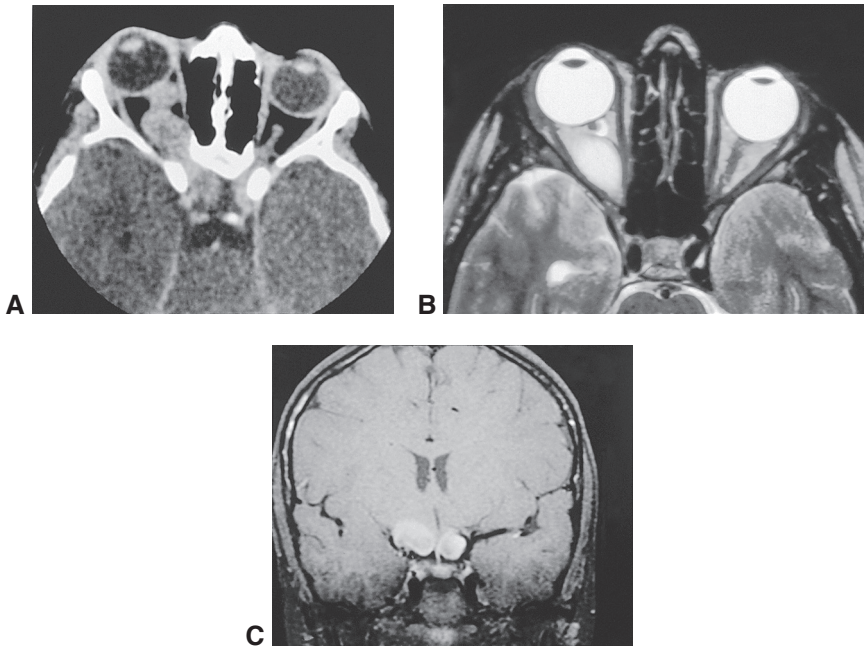


Figure 4-15 Optic pathway glioma. **A**, Contrast-enhanced axial orbital CT scan shows a right optic nerve glioma. The optic nerve is enlarged and kinked and demonstrates mild hypodense cystic change centrally. The tumor extends intracranially. **B**, T2-weighted axial MRI scan (non-contrast-enhanced) of the orbits shows an enlarged, hyperintense, globular glioma of the right optic nerve. **C**, T1-weighted coronal MRI scan shows prominent enlargement at the junction of the optic nerves and chiasm.

asymmetric cases, along with a typical optic nerve–related visual field defect. Optociliary shunt vessels may be present on the affected ONH, although they are observed less commonly than with ONSMs. Diagnosis is confirmed by neuroradiologic findings (see Table 4-8).

In patients with neurofibromatosis 1 (NF1), the prevalence of OPG is 7.8%–21%. In contrast, in patients with OPG, the prevalence of NF1 is 10%–70%. The wide variance probably relates to referral bias, differences in neuroimaging detection rates, and criteria for diagnosis. Similarly, the relationship between NF1 and the behavior of OPG is unclear, although patients with NF1 may have a more benign prognosis. Neurofibromatosis is discussed further in Chapter 14 of this volume and in BCSC Section 6, *Pediatric Ophthalmology and Strabismus*.

As with ONSMs, biopsy of OPGs is generally not required, because the advent of high-resolution neuroimaging has improved diagnostic accuracy, and biopsy of the optic nerve substance may cause additional vision loss.

OPGs involving the chiasm may show bitemporal or bilateral optic nerve–related visual field defects. Involvement of the chiasm (as with any tumor) may produce see-saw nystagmus or a monocular shimmering nystagmoid oscillation (pseudo-spasmus nutans). Large tumors may cause obstructive hydrocephalus with elevated ICP, headache, and papilledema. Involvement of the hypothalamus may result in precocious puberty or diencephalic syndrome.

There is no universally accepted treatment of OPGs. Observation is indicated for patients with relatively good vision and stable radiographic appearance. Most patients show stability or very slow progression over years and sometimes show spontaneous regression. Chemotherapy is offered as the initial treatment for patients with severe vision loss at presentation or evidence of progression. Radiotherapy is controversial because of inconclusive results and potential complications, including panhypopituitarism and cognitive impairment. Surgical excision may be indicated in patients with severe vision loss associated with disfiguring proptosis. Surgery has been suggested to prevent advancement into the chiasm; however, such extension is rare. Hydrocephalus may require CSF shunting.

Malignant gliomas of the anterior visual pathway, or *malignant optic gliomas of adulthood* (MOGAs), are rare neoplasms that almost always occur in adulthood. The mean age on presentation is in the 60s, and there is no gender predilection. Vision loss is often very rapid. Patients may present with acute-onset periorbital pain; in this scenario, these tumors may be misdiagnosed as optic neuritis or NAION. With unilateral lesions, the second eye invariably becomes involved (via the chiasm) within weeks. The ONH appears normal or pale at presentation in most cases, but ONH edema and retinal obstruction resulting in venous stasis retinopathy or CRVO can also occur. When the tumor originates in the distal portion of the optic nerve or the optic chiasm, vision loss may be simultaneously bilateral and associated with a pale or normal-appearing ONH.

An MRI scan most often shows diffuse intrinsic enlargement and enhancement of the affected optic nerves, chiasm, and optic tracts, with inhomogeneity due to cystic spaces within the tumor. Occasionally, a large exophytic component may encroach on the suprasellar cistern. Histologically, MOGAs are classified as either anaplastic astrocytomas or

glioblastoma multiforme. Although radiotherapy and chemotherapy have been attempted, treatment is rarely successful, with blindness usually developing 2–4 months after onset of vision loss. The tumor is aggressively infiltrative, and death from hypothalamic and brainstem involvement usually occurs within 12 months.

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Thyroid eye disease

Thyroid eye disease (TED) often presents with progressive enlargement of extraocular muscles or orbital fat hypertrophy. In rare cases, progressive proptosis can stretch the optic nerve and cause dysfunction. The extraocular muscles can also enlarge, causing compression of the optic nerve at the orbital apex (Fig 4-16). Patients usually present with associated signs (eg, eyelid retraction and lid lag) and may show signs of orbital congestion (eg, eyelid and conjunctival edema) in addition to proptosis. However, some patients demonstrate only minimal orbital findings.

The vision loss associated with TED is usually slowly progressive, insidious, and bilateral. Dyschromatopsia may be an early sign of optic neuropathy. Visual field testing results show central or diffuse depression, and an RAPD is present when the optic neuropathy is asymmetric or unilateral. The ONH is commonly normal but may be mildly edematous. Optic atrophy may be present in chronic cases.

Use of systemic steroids in the acute phase reduces compression on the optic nerve. In some cases, surgical decompression of the posterior orbit is required. The use of radiation therapy alone is controversial and is not indicated for the treatment of acute optic neuropathy (unless it is combined with systemic steroids). TED is discussed at greater length in BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*.

Infiltrative optic neuropathy

Infiltration of the optic nerve by neoplastic or inflammatory cells causes progressive, often severe, vision loss. This visual dysfunction, which is often associated with pain, progresses over days to weeks, with or without other cranial nerve involvement. The optic neuropathy may present in 1 or both eyes and can herald systemic disease. With retrobulbar infiltration, the ONH may initially appear normal. In cases of ONH edema, the cellular infiltrate creates a swollen appearance that may be distinct from that of simple edema (see Fig 4-13). The presence of vitreous cells or peripheral vasculitis may signal an infiltrative process. The most common causes of infiltration include leukemia, lymphoma, syphilis, and granulomatous inflammatory processes such as fungal infections, sarcoidosis, or tuberculosis. Metastasis to the optic nerve is rare, usually occurring from breast or lung carcinoma. Carcinomatous infiltration of the meninges at the skull base may cause not only

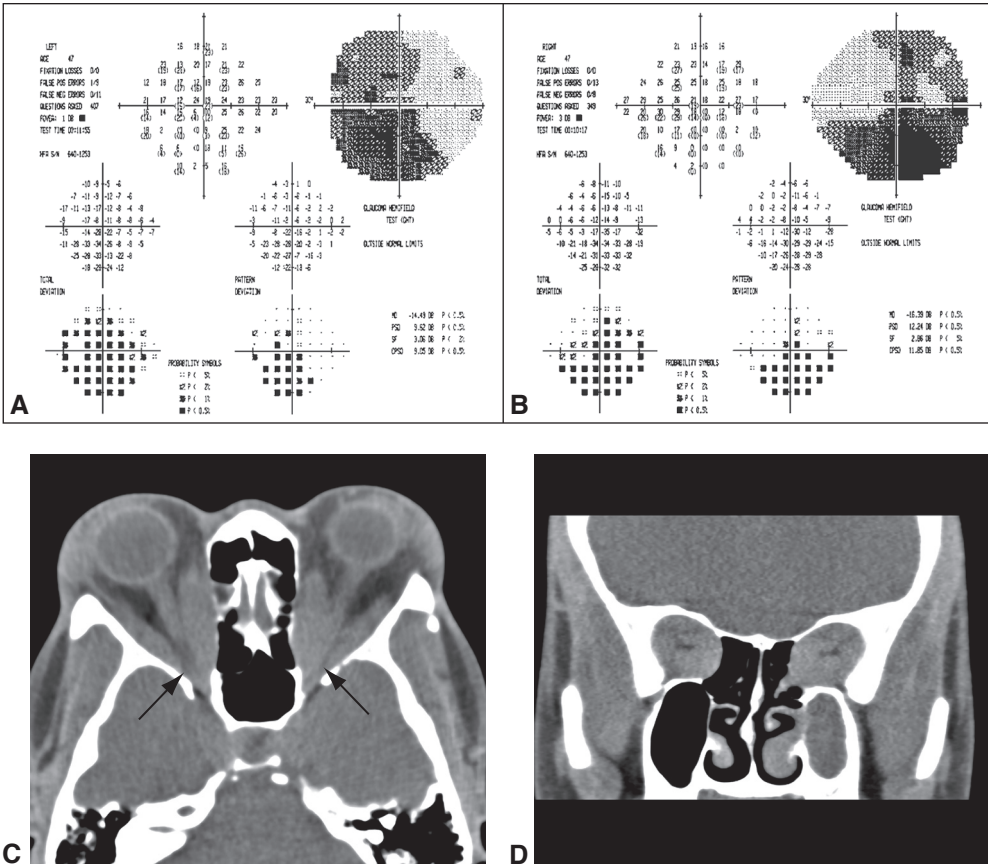


Figure 4-16 Thyroid eye disease (TED) in a 48-year-old man with a 6-month history of weakness, gradual swelling around the eyes, and progressively decreased visual acuity over the prior month. Visual acuity was 20/200 OD and 20/80 OS, with a mild right afferent pupillary defect. **A, B**, Automated perimetry testing shows bilateral central and inferior visual field loss. Axial (**C**) and coronal (**D**) CT scans show the optic nerve becoming compressed (arrows in **C**) by enlarged extraocular muscles. Enlargement of extraocular muscle in TED typically spares the muscle tendon. (Parts **A, B** courtesy of Steven A. Newman, MD; parts **C, D** courtesy of Michael S. Lee, MD.)

vision loss, but also progressive involvement and dysfunction of multiple cranial nerves in 15%–40% of cases. Onset may precede, coincide with, or follow diagnosis of the underlying malignancy.

Evaluation of cases of suspected infiltrative optic neuropathy should include an MRI of the brain and orbits with fat suppression and use of gadolinium contrast to rule out compressive lesions and to confirm pachymeningeal or meningeal infiltration. The MRI scan may show diffuse thickening and enhancement of the dura and the surrounding subarachnoid space in affected regions, including the optic nerve sheaths; however, abnormalities may not be visible in the early stages. Serologic testing includes screening tests for the myeloproliferative, inflammatory, and infectious disorders. Finally, CSF analysis may reveal malignant cells, an elevated white blood cell count, and elevated protein levels

consistent with a neoplastic, infectious, or inflammatory cause. The sensitivity of a single lumbar puncture is low, and repeat testing is often necessary. Securing the correct diagnosis is essential to ensure timely treatment and to prevent life-threatening complications.

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Hereditary optic neuropathies

Leber hereditary optic neuropathy LHON typically affects boys and men aged 10–30 years, but it may occur much earlier or later in life (the possible age range is 1–86 years of age). Symptomatic women account for only 10%–20% of cases. The syndrome presents with acute, painless, sequential, and severe vision loss (visual acuity, <20/200) associated with central or cecocentral visual field impairment (Fig 4-17). The classic fundus appearance triad includes

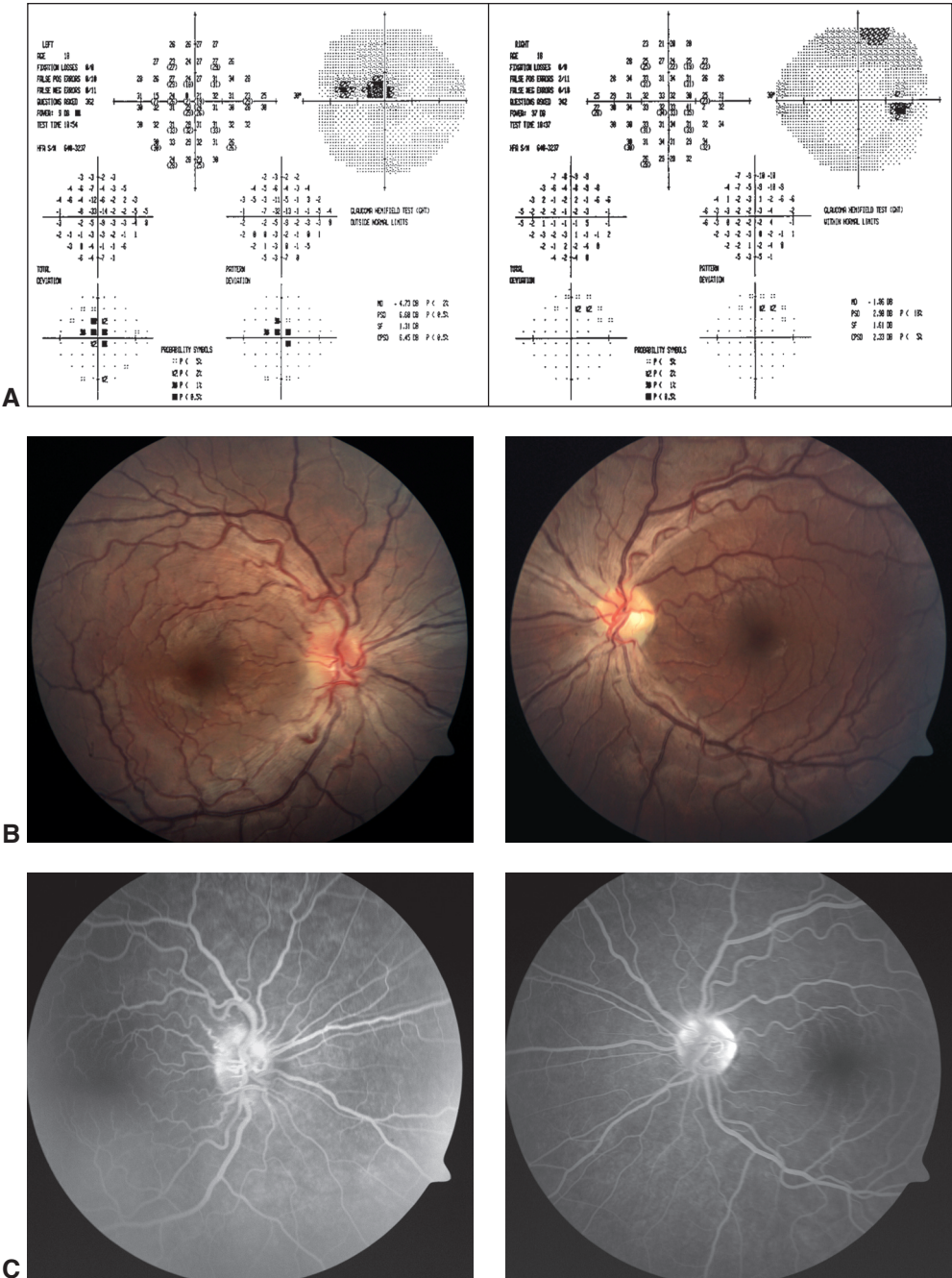
1. hyperemia and elevation of the ONH, with thickening of the peripapillary retina; although the ONH appears swollen, it does not leak on fluorescein angiography (“pseudooedema”)
2. peripapillary telangiectasia
3. tortuosity of the medium-sized retinal arterioles

These findings can be observed before vision loss begins. The fundus can also appear entirely normal on presentation. The unaffected eye typically becomes symptomatic within weeks to months; however, although rare, the interval between initial and fellow eye involvement can be longer (up to 8 years).

LHON results from a mitochondrial DNA mutation, most frequently at the 11778 position, less commonly at the 3460 or 14484 locations. Results of blood testing for these mutations confirm the diagnosis, permit genetic counseling, and provide information about prognosis. Children and adult patients with the 14484 mutation have a higher chance (up to 65%) of late spontaneous improvement in central visual function, whereas those with the 11778 mutation have a lower chance (estimated at 4%).

The point mutation is transmitted by mitochondrial DNA, which is inherited only from the mother; thus, only women transmit the disease. As mitochondria replicate, the mitochondrial DNA is variably divided among the progeny cells (heteroplasmy). However, the vast majority of LHON cases are homoplasmic. Family history may be negative because of a de novo mutation or lack of phenotypic expression. Not all men with affected mitochondria experience vision loss, and affected women experience visual symptoms only infrequently. The reasons for this selective male susceptibility remains unknown.

The differential diagnosis of LHON includes all other causes of optic neuropathies, particularly optic neuritis, compressive optic neuropathy, and infiltrative optic neuropathy. For patients with a negative family history, neuroimaging should be performed. Mitochondrial testing for the 3 primary mutations is commercially available. Occasionally,



patients demonstrate cardiac conduction abnormalities or other mild neurologic deficits that warrant further evaluation.

No treatment has been shown to be effective for LHON. Corticosteroids are not beneficial. The effect of idebenone on visual outcome remains controversial. Tobacco use or excessive alcohol intake may stress mitochondrial function and thus contribute to vision loss; therefore, patients with LHON should avoid the use of tobacco and curtail alcohol consumption.

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Autosomal dominant optic atrophy The most common hereditary optic neuropathy (estimated prevalence, 1:50,000) is autosomal dominant optic atrophy (ADOA), which has a dominant inheritance pattern with variable penetrance and expression. Genetic linkage studies have localized an ADOA gene (*OPA1*) to a region on chromosome 3. The *OPA1* protein is widely expressed and most abundant in the retina. It encodes dynamin-related GTPase, which is anchored to mitochondrial membranes; thus, mutations result in loss of mitochondrial membrane integrity and function, with subsequent retinal ganglion cell degeneration and optic atrophy.

ADOA usually presents in the first decade of life, with insidious onset of vision loss; it is often first detected during routine school vision screenings. Involvement is usually bilateral and relatively symmetric. At detection, visual acuity loss is usually mild to moderate, ranging from 20/30 to 20/60, although acuity may decline progressively. Most patients preserve a visual acuity greater than 20/200. Color vision deficits, usually tritanopia (blue-yellow), are invariably present. These patients may pass evaluation with the Ishihara color plates, which test red-green deficits. Tritanopia detection may require testing by Hardy-Rand-Rittler plates or the Farnsworth panel D-15 or D-100 test. In most cases, visual field testing demonstrates central or cecocentral loss. The defects typically do not respect the vertical midline. Affected ONHs usually show focal, wedge-shaped temporal optic atrophy (Fig 4-18), but diffuse pallor can occur.

The clinical diagnosis is based on the examination findings and negative neuroimaging results (which should be performed in all suspected cases). Genetic testing is commercially available but does not test for all mutations that cause ADOA, so it is helpful only when positive. The clinical course is generally one of stability or very slow progression over the patient's lifetime (loss of approximately 1 Snellen line per decade). No treatment is available.

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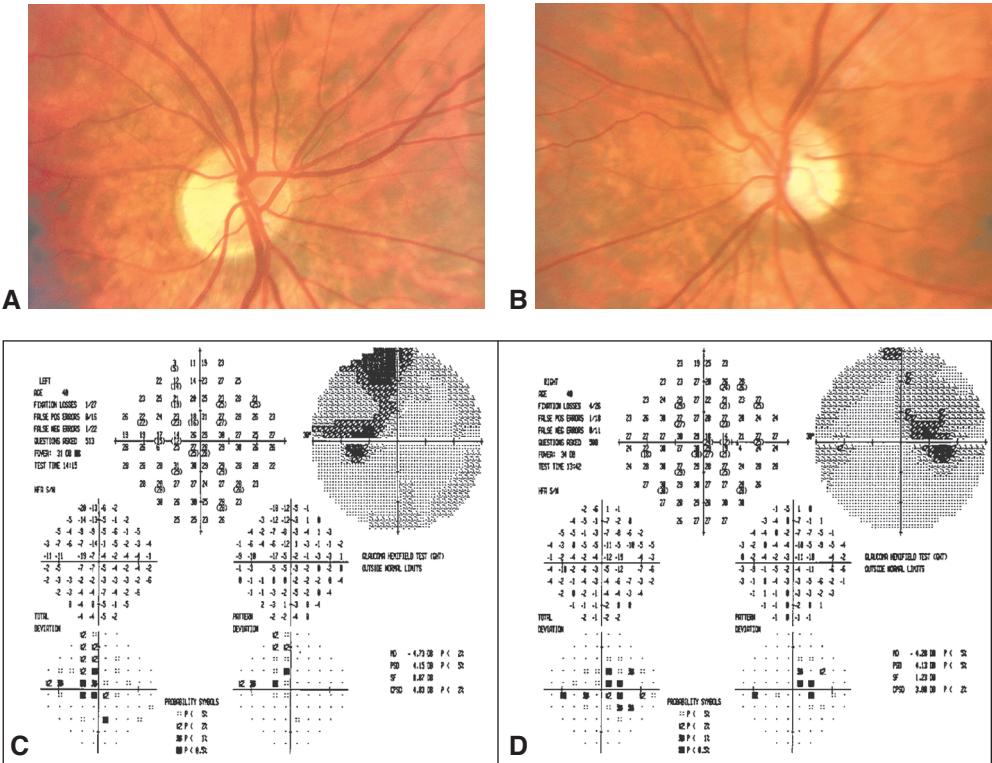


Figure 4-18 Autosomal dominant optic atrophy findings in a 34-year-old man who had been aware of difficulty reading the blackboard in fourth grade, with a mild, gradual decrease in visual acuity bilaterally since then. **A, B**, Fundus photographs of ONHs show temporal atrophy and papillomacular nerve fiber layer dropout. **C, D**, Visual field patterns demonstrate bilateral cecocentral scotomata, which extend superotemporally. (Courtesy of Steven A. Newman, MD.)

Glaucoma

Patients with glaucoma do not usually note impaired vision until central vision is affected. Primary open-angle glaucoma is usually characterized by slowly progressive arcuate and peripheral visual field loss, sparing fixation until late in the course. Glaucoma is also distinguished from other optic neuropathies by the following features: preserved color vision, characteristic excavation of the optic cup (with increased diameter and depth of the physiologic cup, often with focal notching at the inferior or superior pole), and lack of pallor of the neuroretinal rim (until the disease is advanced). All aspects of glaucoma are discussed at length in BCSC Section 10, *Glaucoma*.

Excavation of the ONH may also be present in compressive, hereditary (LHON, ADOA), and severe ischemic (AAION) processes. However, in these cases, the nerve is pale in addition to being cupped. Chiasmal compressive lesions typically produce temporal (hemianopic) rather than nasal visual field loss. These other optic neuropathies affect visual acuity and color vision, which are late findings in glaucoma. In addition, the ONH may demonstrate early and more prominent pallor, with less severe excavation and notching than in glaucoma (Fig 4-19).

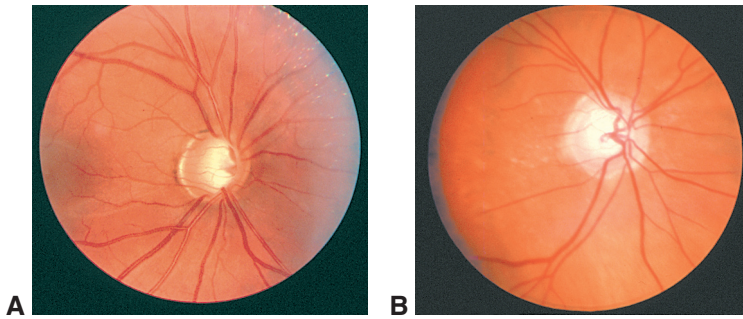


Figure 4-19 Optic nerve excavation. **A**, Fundus photograph of *glaucomatous* damage; the remaining temporal rim of neuroretinal tissue generally remains a relatively normal pink color despite severe excavation. **B**, Fundus photograph of *nonglaucomatous* damage; the rim is pale relative to the degree of excavation. (Courtesy of Anthony C. Arnold, MD.)

Toxic or nutritional optic neuropathy

Optic neuropathies resulting from toxic exposure or nutritional deficiency constitute a heterogeneous group of conditions that are generally characterized by gradual, progressive, and painless vision loss that is bilateral and symmetric. Initial findings may include a subtle depression of central vision sensitivity on Amsler grid testing or perimetry testing focused within the central 10°. As the disturbance becomes progressively more severe, however, central vision loss worsens, accompanied by a decrease in visual acuity and color vision and a central scotoma (Fig 4-20). Occasionally, a more rapid onset of decreased vision may occur. Optic atrophy eventually develops if the cause is not corrected. In rare cases, the ONHs may exhibit mild to moderate edema on presentation. Diagnosis requires obtaining a thorough patient history for possible medication or other toxic exposure, substance abuse, or dietary deficiency (as may occur after bariatric surgery or colectomy). Causation is usually multifactorial, and definite proof of optic nerve toxicity by a single toxic agent or nutritional deficiency is rare.

The most commonly implicated agents in the development of toxic optic neuropathies include methanol, ethylene glycol, organic solvents, lead (in children), tobacco (usually cigars), ethambutol, linezolid, amiodarone, disulfiram, ciprofloxacin, and the antineoplastic drugs cisplatin and vincristine. Because it may contribute to malnutrition, ethanol abuse is probably associated indirectly with optic neuropathy. Methanol and ethylene glycol toxicity cause a rapid onset of severe bilateral vision loss with prominent ONH edema.

Other medications that are now recognized as potential causes of toxic optic neuropathies include interferon and anti-tumor necrosis factor alpha (anti-TNF- α) agents (eg, etanercept, infliximab, and adalimumab). TNF- α antagonists may cause an acute demyelinating optic neuritis. Some toxic optic neuropathies are more commonly associated with ONH swelling. Amiodarone toxicity may present with bilateral vision loss and ONH edema. It may be differentiated from NAION by its subacute onset, bilaterality, diffuse rather than altitudinal visual field loss, and slow resolution of ONH edema over months after discontinuance of the medication. Interferon- α administration has been reported as a cause of bilateral NAION. PDE5-inhibitor use has been associated with an increased risk of NAION, but this association is controversial.

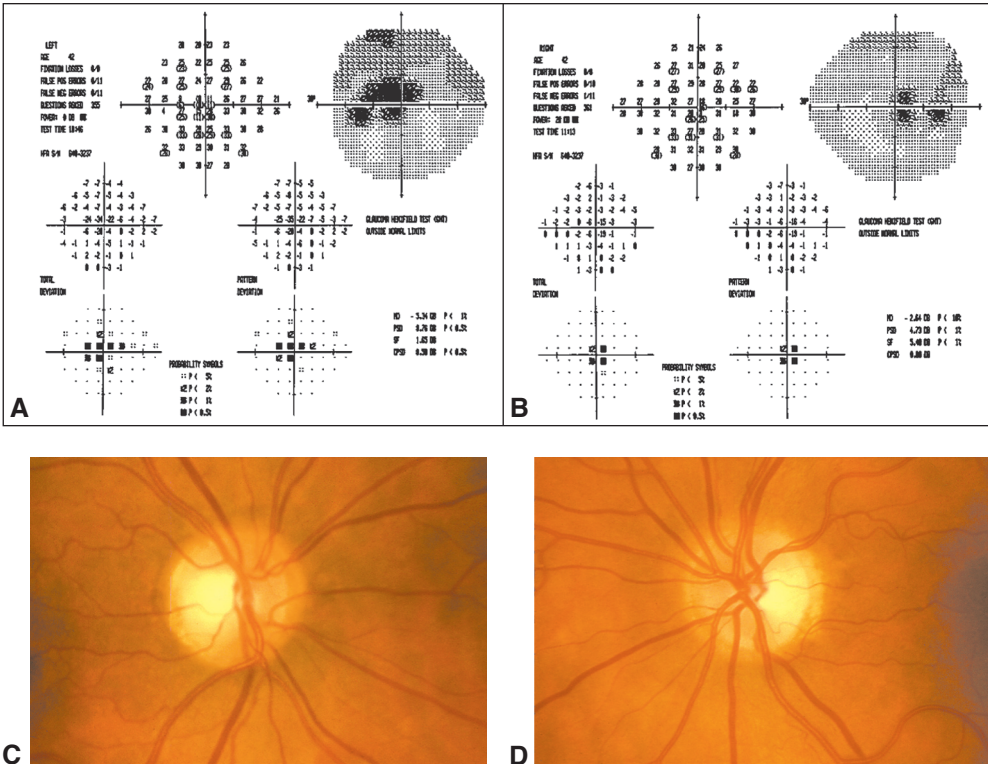


Figure 4-20 Optic neuropathy caused by nutritional deficiency in a 42-year-old woman with a history of 4 bowel resections who presented with bilateral blurred vision and trouble recognizing colors. Visual acuity was 20/70 OD and 20/200 OS, without an afferent pupillary defect. **A, B,** Visual field results demonstrate a cecocentral scotoma on the left and a relative central scotoma on the right. **C, D,** Fundus appearance shows mild temporal optic atrophy in both eyes, with papillomacular nerve fiber layer dropout. After the patient was treated with multivitamins and hydroxycobalamin injections, the visual field defects resolved completely and visual acuity returned to 20/20. (Courtesy of Steven A. Newman, MD.)

Dietary deficiencies of vitamin B₁₂, copper, folate, and thiamine may cause optic neuropathy, but exact deficiencies are difficult to identify in cases of suspected nutritional optic neuropathy. Tobacco use has long been implicated in optic nerve dysfunction, but the evidence to support this implication is questionable. Diagnosing nutritional optic neuropathy may be difficult, particularly in patients whose symptoms are vague and who show little objective abnormality. Obtaining a careful and detailed dietary history may help, but ethanol abusers may obscure or falsify details of food and ethanol ingestion. Specific vitamin deficiencies are detected only infrequently on blood testing. It may be challenging to implicate a specific medication in patients using multiple medications.

The differential diagnosis of toxic or nutritional optic neuropathies includes subtle maculopathies and hereditary, compressive, demyelinating, and infiltrative optic neuropathies. Fluorescein angiographic studies, hematologic and serologic testing, and CSF

analysis (in rare cases) are performed in questionable cases. Neuroimaging should be performed routinely to rule out a compressive etiology.

The goal of treatment is to reverse the inciting cause: stopping medication or substance abuse and resolving dietary deficiencies. Prognosis for vision recovery is good if optic atrophy has not supervened; however, recovery is highly variable. Improvement of vision typically occurs slowly over several months.

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Traumatic optic neuropathy

The optic nerve may be damaged by trauma to the head, orbit, or globe. *Direct* traumatic optic neuropathy (TON) may be caused by injury to the nerve itself or by laceration with bone fragments (Fig 4-21) or other foreign bodies. Injuries may also cause compressive optic neuropathy secondary to intraorbital or intrasheath hemorrhage. Indirect trauma to the optic nerve is more common than direct optic nerve injury. *Indirect* TON may occur even with relatively minor head injury. The trauma involves the frontal or maxillary bone, and the transmitted forces damage the optic nerve at the orbital apex. Avulsion of the nerve may also occur. The pathophysiology presumably involves shear forces on the nerve and possibly its vascular supply in the optic canal. Vision loss is typically immediate and often severe (24%–86% of patients have no light perception at presentation). External evidence of injury may be scarce. An RAPD is invariably present if there

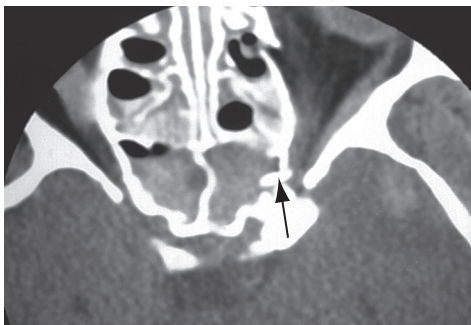


Figure 4-21 CT scan of an 18-year-old involved in a severe motor vehicle accident. He had noted decreased visual acuity on the left side. The CT scan shows fracture in the area of the left optic canal, with a bone fragment (arrow) impinging on the left optic nerve. Visual acuity improved after transethmoidal decompression of the canal. (Courtesy of Steven A. Newman, MD.)

is unilateral vision loss. Although the ONH usually appears normal at onset, it becomes atrophic within 4–8 weeks.

Management of suspected TON requires neuroimaging (head, orbit, and facial CT) to assess the extent of injury and to detect any associated intracranial and facial injury, intraorbital fragments, or hematoma. Orbital or cranial surgery may be necessary but may not affect the prognosis for the optic nerve. Therapy for indirect TON is controversial. Although the prognosis for vision recovery has generally been regarded as poor, numerous reports describe occasional spontaneous recovery of some visual function. The International Optic Nerve Trauma Study, a nonrandomized, multicenter, comparative analysis of treatment outcomes, found no clear benefit for treatment with intravenous corticosteroids or optic canal decompression, and no consensus exists for their use, whether alone or in combination. The Corticosteroid Randomization After Significant Head Injury (CRASH) study enrolled more than 10,000 patients with head injuries and compared results from treatment with high-dose corticosteroids (2 g methylprednisolone intravenous and then 0.4 g for 48 hours in a 20 mL/hour infusion) versus placebo within an 8-hour window after trauma. The study was terminated early after initial analysis revealed that the corticosteroid group had a statistically significantly higher rate of mortality than the placebo group. This finding raised safety concerns regarding the use of high-dose corticosteroids in the treatment of TON, particularly in patients with severe head trauma.

Carta A, Ferrigno L, Salvo M, Bianchi-Marzoli S, Boschi A, Carta F. Visual prognosis after indirect traumatic optic neuropathy. *J Neurol Neurosurg Psychiatry*. 2003;74(2):246–248.

Edwards P, Arango M, Balica L, et al; CRASH trial collaborators. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury—outcomes at 6 months. *Lancet*. 2005;365(9475):1957–1959.

Levin LA, Beck RW, Joseph MP, Seiff S, Kraker R. The treatment of traumatic optic neuropathy: the International Optic Nerve Trauma Study. *Ophthalmology*. 1999;106(7):1268–1277.

Steinsapir KD, Goldberg RA. Traumatic optic neuropathy: an evolving understanding. *Am J Ophthalmol*. 2011;151(6):928–933;e2. <http://www.sciencedirect.com/science/article/pii/S0002939411001516>. Published June 2011. Accessed January 31, 2017.

Optic disc drusen

Optic disc drusen (ODD), also known as *hyaline* or *colloid bodies*, represent refractile, often calcified nodules located within the optic nerve head (Fig 4-22). The reported prevalence ranges from 0.34% (clinical) to 2% (autopsy). ODD occur with equal frequency in males and females but rarely affect nonwhites. They are often bilateral (75%–86%) but can be asymmetric. They may be isolated or dominantly inherited.

The pathophysiology of ODD is unclear. Most theories suggest a process of impaired ganglion cell axonal transport, probably related to a small scleral canal and mechanical obstruction. Metabolic abnormalities associated with impaired transport may result in intra-axonal mitochondrial damage. The drusen represent the product of deteriorating axons, which extrude their contents into the interstitial space. Over time, the extruded material congeals and calcifies. ODD may be associated with retinitis pigmentosa and pseudoxanthoma elasticum.

Although most patients with ODD do not experience symptoms, some (8.6%) may have transient visual obscurations if there is associated ONH swelling. In rare cases, vascular complications (eg, flame hemorrhage, AION, or peripapillary subretinal neovascularization) occur. Nerve fiber bundle defects occur in 75%–87% of cases, but most go

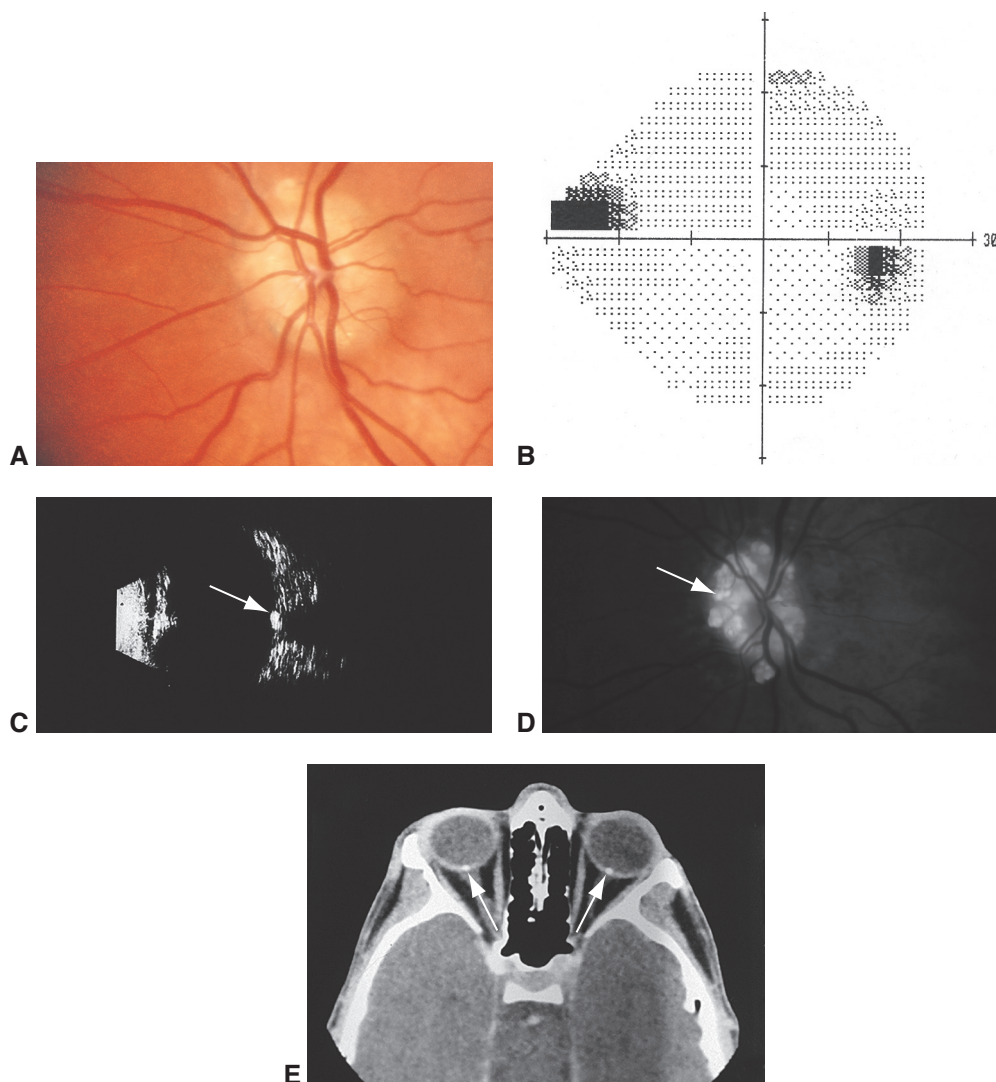


Figure 4-22 Optic disc drusen. **A**, Fundus photograph showing blurred ONH margin with scalloped edge, refractile bodies on the ONH surface and at the superior pole, mild pallor, and no obscuration of retinal blood vessels. **B**, Visual field patterns confirmed the presence of a nasal step produced by drusen involving the right ONH. **C**, B-scan ultrasonogram demonstrating focal, highly reflective (due to calcification) elevation within the ONH (arrow), which persists when the gain is decreased. **D**, Preinjection fundus photograph demonstrating autofluorescence (arrow). **E**, CT scan of the orbits. Calcified ODD are visible bilaterally at the posterior globe–optic nerve junction (arrows). (Part A courtesy of Steven A. Newman, MD; part B courtesy of Michael S. Lee, MD; parts C, E courtesy of Anthony C. Arnold, MD; part D courtesy of Hal Shaw, MD.)

unnoticed by the patient. Visual field defects either remain stable or worsen very slowly. Visual field patterns should be monitored over time. Visual acuity rarely declines; thus, evaluation for other causes of vision loss should be performed if visual acuity declines or progressively worsens. The location of visible drusen does not necessarily correlate with the location of visual field loss. An RAPD may be present in patients with asymmetric visual field loss.

The ONHs of patients with ODD appear elevated and small in diameter, with indistinct or irregular margins and associated anomalous vascular branching patterns. Blurring of the ONH margin arises from axoplasmic stasis in the axons deep within the ONH, creating a yellowish, hazy appearance that obscures the border between ONH and retina but leaves the view of the retinal vessels intact. This appearance contrasts with the whitish, fluffy, striated appearance of RNFL edema in true papilledema. With ODD, the ONH does not show hyperemia or dilation of the surface microvasculature.

In children, ODD are initially buried, becoming more visible over the years. When visible, ODD appear as round, whitish-yellow refractile bodies. Frequently present at the nasal ONH margin, surface drusen may have a scalloped appearance. Occasionally, they are located within the RNFL just adjacent to the ONH.

Ancillary testing may be useful in differentiating ODD from ONH edema (eg, papilledema) (see Fig 4-22):

- *B-scan ultrasonography* may differentiate calcified drusen from papilledema in 2 ways. First, ODD are highly reflective. Calcified drusen maintain this high echogenicity with lowering of the ultrasound gain. With papilledema, the signal intensity decreases along with the remainder of the ocular signal. Ultrasonography may help identify drusen in suspected cases, but this technique may not detect noncalcified, buried ODD. Second, with papilledema, the intraorbital portion of the optic nerve is typically widened and will decrease in width with prolonged lateral gaze (the so-called *30° test*); ODD do not produce widening of the intraorbital nerve (see Fig 4-22C).
- *Autofluorescence* is also an effective method for distinction. Drusen that are close enough to the ONH surface demonstrate *autofluorescence*, in which refractile bodies appear brightly visible on preinjection images using the fluorescein filter (see Fig 4-22D).
- *Fluorescein angiography* may show early diffuse hyperfluorescence, with late leakage overlying and adjacent to the ONH in true ONH edema. Conversely, ODD do not cause leakage. In cases where the ODD are associated with ONH edema, however, there may be leakage on fluorescein.
- *Neuroimaging* may be indicated in rare cases to rule out an intracranial or optic nerve tumor and to attempt direct confirmation of calcified drusen. CT is superior to an MRI scan for detection of drusen because calcium is poorly imaged by MRI. Calcified drusen produce a bright, easily detected signal at the junction site of the globe and optic nerve on CT (see Fig 4-22E).
- *OCT* using a line scan through the optic nerve can show the discrete hyperreflective drusen. Although newer OCT techniques such as enhanced depth imaging (EDI) offer improved imaging of drusen, this is not evident in all cases.

With chronic papilledema, refractile bodies occasionally develop on the ONH surface, simulating ODD (see Fig 4-7). These lesions (probably residual exudate) typically form near the temporal margin of the ONH rather than within its substance, are usually smaller than ODD, and disappear with resolution of the papilledema.

Astrocytic hamartomas of the retina, most common in tuberous sclerosis and NF, may take the form of so-called *mulberry lesions*. When located adjacent to the ONH, they may closely resemble ODD, and they were initially termed *giant drusen of the optic disc* (see Fig 4-4). In contrast to true ODD, ONH hamartomas

- originate at the ONH margin, with extension to the peripapillary retina
- arise in the inner retinal layers and typically obscure retinal vessels
- may have a fleshy, pinkish component
- do not autofluoresce and may show tumor-like vascularity on fluorescein angiography

Auw-Haendrich C, Staubach F, Witschel H. Optic disk drusen. *Surv Ophthalmol*. 2002;47(6):515–532.

Congenital optic nerve head anomalies

Optic nerve hypoplasia Visual acuity in eyes with optic nerve hypoplasia ranges from 20/15 with minimal visual field defects to no light perception. However, nearly all eyes affected by this condition have visual field loss, and 56%–92% of patients have bilateral involvement. The ONH is small, usually one-half to one-third of normal diameter; subtle cases may require a comparison of the 2 eyes. Comparing the horizontal ONH diameter with the ONH–macula distance may help in detection. Retinal vessel diameter may seem large relative to the ONH size, and the vessels may appear tortuous. The ONH may seem pale, gray, or (less commonly) hyperemic and may be surrounded by a yellow peripapillary halo, which in turn is bordered by a ring of increased or decreased pigmentation (the *double-ring sign*) (Fig 4-23).

Unilateral or bilateral optic nerve hypoplasia may be associated with midline or hemispheric brain defects, endocrinologic abnormalities (deficiency of growth hormone and other pituitary hormones), and congenital suprasellar tumors. Skull-base defects may be associated with basal encephaloceles. The syndrome of optic nerve hypoplasia, absent septum pellucidum, and pituitary dwarfism (septo-optic dysplasia or de Morsier



Figure 4-23 Optic nerve hypoplasia. The small ONH is surrounded by a relatively hypopigmented ring of tissue (double-ring sign). The retinal vessels have normal appearance. (Reprinted from Kline LB, Foroozan R, eds. *Optic Nerve Disorders*. 2nd ed. *Ophthalmology Monographs* 10. New York: Oxford University Press, in cooperation with the American Academy of Ophthalmology; 2007:158.)

syndrome) is the most common. The corpus callosum may be thinned or absent. An MRI scan is recommended in all cases of optic nerve hypoplasia, and endocrinologic evaluation is necessary, because hypoglycemic seizures or growth retardation may develop without appropriate treatment. Recognized teratogens associated with optic nerve hypoplasia include quinine, ethanol, and anticonvulsants. A variant called superior segment hypoplasia occurs most often in children of mothers with diabetes mellitus; the affected eyes have a corresponding inferior visual field defect. For further details on optic nerve hypoplasia, see BCSC Section 6, *Pediatric Ophthalmology and Strabismus*.

Congenital tilted disc syndrome Congenital tilted disc syndrome is usually bilateral (80%) and should not be confused with simple myopic tilted ONHs with temporal crescent. The congenital syndrome produces an inferonasal colobomatous excavation of the nerve tissue, often associated with thinning of adjacent RPE and choroid. The remaining superotemporal portion of the ONH remains relatively intact; the ONH appears tilted around a predominantly horizontal axis. The superior portion can sometimes seem elevated, simulating mild edema (Fig 4-24). The retinal vessels are often nasalized. The visual field defects may mimic those of chiasmal compression but are differentiated by their failure to respect the vertical midline and their partial improvement with myopic refractive correction.

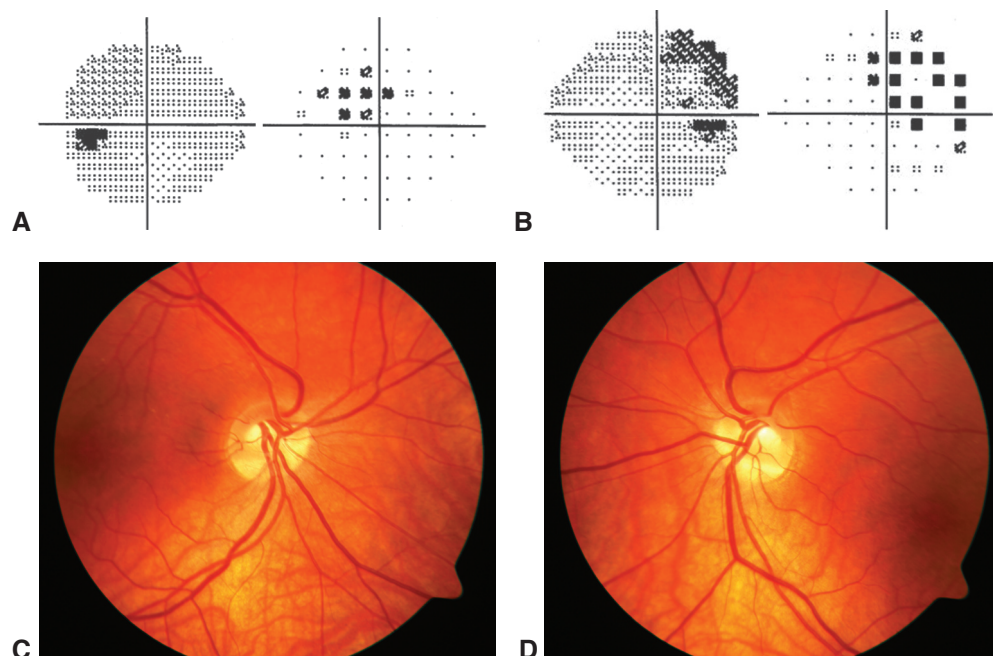


Figure 4-24 Congenital tilted disc syndrome. Visual field testing results (**A, B**) show bilateral relative superotemporal defects that do not respect the vertical midline. Fundus photographs show bilateral tilted ONHs in the right eye (**C**) and in the left eye (**D**). (Parts A, B courtesy of Anthony C. Arnold, MD; parts C, D courtesy of Sophia M. Chung, MD.)

Excavated optic nerve head anomalies Excavated ONH anomalies cover a spectrum of severity, ranging from optic pits through colobomas and dysplastic nerves to the morning glory ONH anomaly:

- An *optic pit* is a depression of the ONH surface that is often gray or white, located inferotemporally, and associated with a mild visual field defect (usually paracentral or arcuate). Serous detachment of the macula develops in 25%–75% of cases, possibly related to liquefied vitreous entering the subretinal space through communication between the optic pit and the macula.
- *Colobomas* of the nerve result from incomplete closure of the embryonic fissure and usually occur inferiorly; they occasionally extend to the adjacent choroid and retina. Visual field defects and an RAPD can occur, depending on the degree of abnormality. Colobomas of other structures, such as iris and choroid, may be present.
- The *dysplastic nerve* of papillorenal syndrome or renal coloboma syndrome appears excavated with absence or attenuation of the central retinal vessels and multiple cilioretinal vessels emanating and exiting from the ONH edge. Visual acuity is often normal, but perimetry may reflect superonasal visual field defects. Controversy exists regarding whether the nerves are colobomatous from incomplete embryonic fissure closure or from a primary dysplasia of the optic nerve. This characteristic optic nerve appearance may indicate renal failure secondary to renal hypoplasia and is linked to mutations in the *PAX2* gene (which are autosomal dominant).
- The *morning glory ONH anomaly* is a funnel-shaped staphylomatous excavation of the optic nerve and peripapillary retina. It is more common in females and usually unilateral. The ONH is enlarged, pink or orange, and either elevated or recessed within the staphyloma. Chorioretinal pigmentation surrounds the excavation, and white glial tissue is present on the central ONH surface. The characteristic feature is the emanation of retinal vessels from the periphery of the ONH. Visual acuity can be normal but is often 20/200 or worse and accompanied by an RAPD. Nonrhegmatogenous serous retinal detachments occur in 26%–38% of cases. Neuroimaging is warranted to evaluate for a basal encephalocele and CNS vascular anomalies.

For additional discussion, see BCSC Section 6, *Pediatric Ophthalmology and Strabismus*.

Brodsky MC. Congenital optic disk anomalies. *Surv Ophthalmol*. 1994;39(2):89–112.

Lee BJ, Traboulsi EI. Update on the morning glory disc anomaly. *Ophthalmic Genet*. 2008; 29(2):47–52.

Nicholson B, Ahmad B, Sears JE. Congenital optic nerve malformations. *Int Ophthalmol Clin*. 2011;51(1):49–76.

Optic Atrophy

The combination of vision loss, an RAPD, and optic atrophy is nonspecific and might represent the chronic phase of any of the optic neuropathies described in this chapter. When historical features and clinical signs do not suggest a specific cause, baseline studies of optic nerve function and a screening workup for treatable causes are usually undertaken. The level of optic nerve function is established by visual acuity determination,

color vision testing, and quantitative perimetry testing. Fundus photography, preferably in stereoscopic views, can be used to document the degree and pattern of atrophy, helping the clinician detect subtle changes in contour over time. RNFL thickness can be monitored using OCT.

Neuroimaging, preferably MRI of the brain and orbits with use of gadolinium contrast and fat suppression, is warranted in any case of optic atrophy without a clear cause. In the appropriate clinical or historical setting, the clinician should pursue laboratory evaluation. Screening for syphilis, vitamin B₁₂ deficiency, folate deficiency, vasculitis, sarcoidosis, and heavy-metal toxicity should be performed for patients without a history or examination finding suggestive of a specific disease. Observation remains reasonable for patients with negative results from testing. However, if the condition worsens or new findings develop, reassessment of the initial testing or additional testing becomes necessary.

Chiasmal Lesions

With the segregation of nasal and temporal retinal fibers at the chiasm, visual field loss due to chiasmal and retrochiasmal lesions is characterized by temporal defects that align along the vertical meridian. The most common visual field defect of chiasmal compression is a bitemporal hemianopia. These defects may appear relative or complete. They may involve the paracentral temporal field alone, and visual acuity is often unaffected until late (Fig 4-25).

In chiasmal syndromes, the ONHs may appear normal initially, even with significant visual field loss. Early on, peripapillary retinal RNFL dropout and mild ONH pallor develop. With progressive damage, the ONHs show typical atrophy, often in the temporal portion of the ONH. Cupping of the ONH may increase. A tumor compressing the chiasm almost never produces ONH edema. Parasellar lesions that involve the chiasm—whether compressing or infiltrating this area—result in gradually progressive, bilateral, often asymmetric vision loss. The peripheral (temporal) visual fields are usually involved first. In any case of bilateral visual field loss, the clinician must carefully evaluate perimetry testing results for respect of the vertical midline. Any of the variations on bitemporal visual field loss (described in the following sections) may occur. An affected optic nerve may cause more central vision loss, with impaired visual acuity, dyschromatopsia, and an RAPD on the affected side. Markedly asymmetric visual field loss without direct optic nerve damage may also produce an RAPD.

Visual Field Loss Patterns

Lesions that injure an optic nerve at its junction with the optic chiasm cause *junctional scotomas*. Diminished visual acuity and central visual field loss occur in the ipsilateral eye, and a temporal hemianopia develops in the opposite eye (Fig 4-26). A unilateral temporal hemianopia that respects the vertical midline, with no involvement of the visual field in the opposite eye (also known as a junctional scotoma of Traquair), can also indicate a

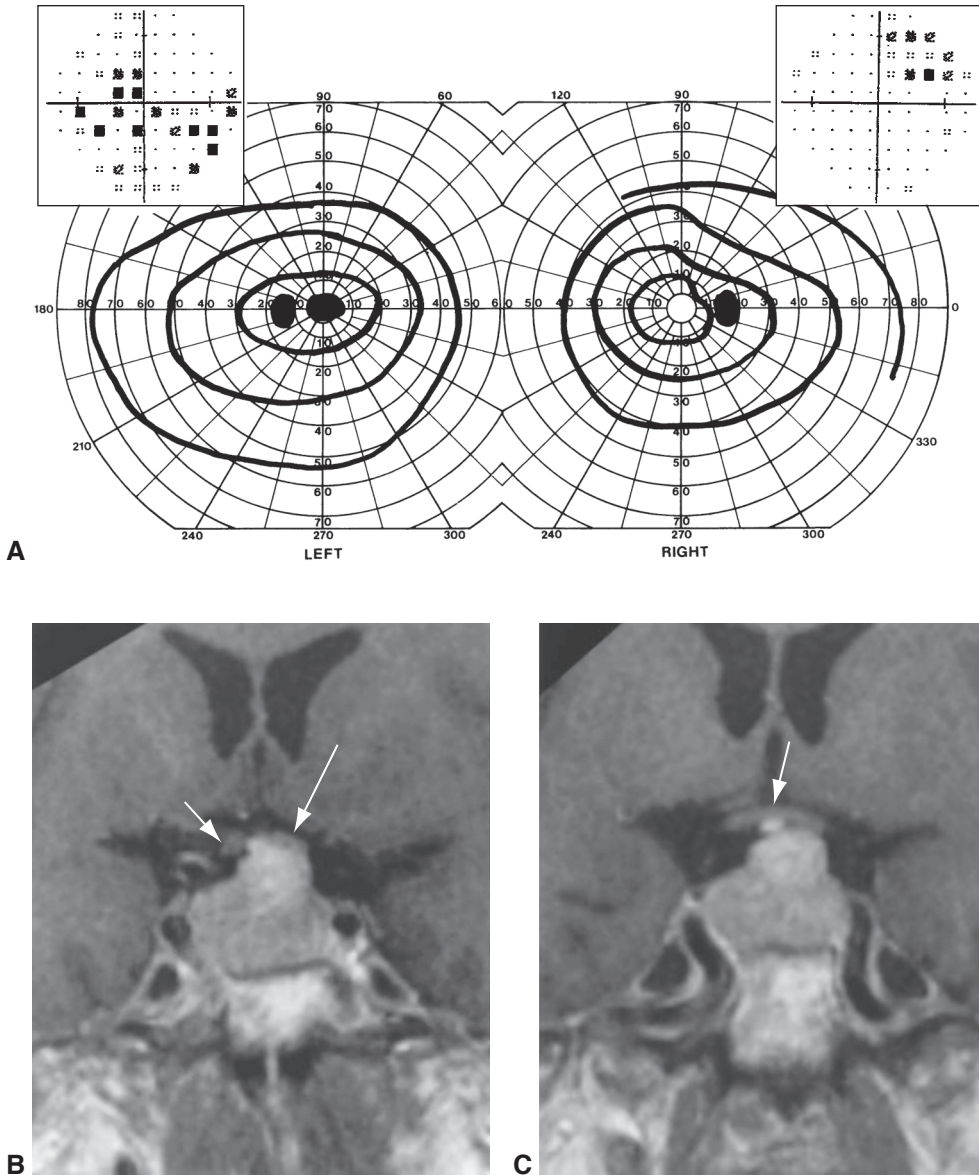


Figure 4-26 Junctional scotoma. **A**, Visual field patterns from kinetic perimetry testing and Humphrey 30-2 program testing (*insets*). Note the central scotoma in the patient's left eye along with the superotemporal depression in his right eye. **B**, **C**, Postcontrast, T1-weighted (TR = 650 ms; TE = 14 ms) MRI scans using a slice thickness of 3 mm. **B**, Coronal image of a section in front of the optic chiasm showing a tumor compressing the prechiasmatic segment of the left optic nerve (*long arrow*) but not the right optic nerve (*short arrow*). **C**, Coronal image at the level of the optic chiasm showing minimal rostral displacement (*arrow*) but no notable direct mass effect. (Reprinted with permission from Karanjia N, Jacobson DM. Compression of the prechiasmatic optic nerve produces a junctional scotoma. *Am J Ophthalmol.* 1999;128(2):256–258.)

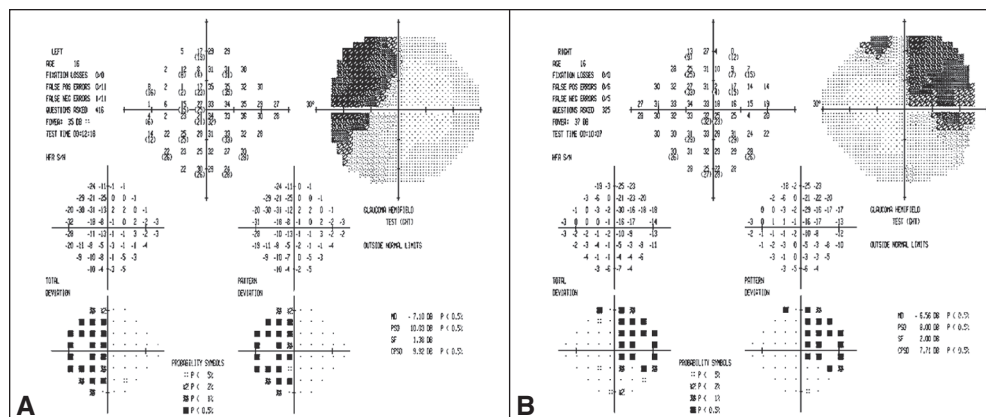


Figure 4-27 Pituitary adenoma. **A, B**, Visual field patterns from a patient with a pituitary tumor, showing bitemporal depression worse superiorly, with margination along the vertical midline. **C**, AT1-weighted coronal MRI scan shows an intrasellar enhancing mass, with extension into the suprasellar cistern and upward displacement and compression of the chiasm (arrow). (Parts A, B courtesy of Steven A. Newman, MD; part C courtesy of Sophia M. Chung, MD.)

Acute hemorrhage or infarction of the pituitary tumor, known as *pituitary apoplexy*, is a potentially life-threatening event heralded by severe headache, nausea, and altered consciousness. Neuro-ophthalmic findings include diplopia and loss of vision or visual field (Fig 4-28). Sudden expansion of the tumor into the adjacent cavernous sinuses can cause dysfunction of CNs III, IV, V, and VI (CN III is most commonly affected). Superior extension causes severe visual loss ranging from normal visual acuity with bitemporal hemianopia to no light perception. Extravasation of blood into the subarachnoid space causes numerous symptoms, including a decreased level of consciousness and vasospasm with secondary stroke. The acute endocrine abnormalities may lead to numerous complications, including adrenal crisis. Therefore, recognition of pituitary apoplexy is crucial so that neurosurgical treatment can be initiated promptly.

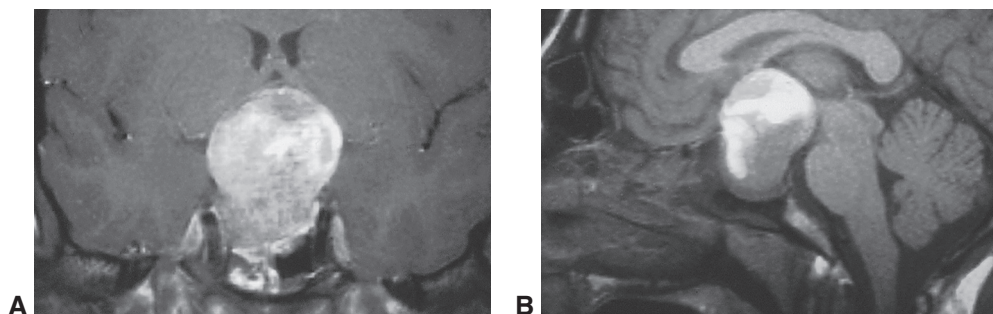


Figure 4-28 Acute compressive optic neuropathy in pituitary apoplexy. Coronal (**A**) and sagittal (**B**) MRI scans show a large pituitary tumor with suprasellar extension. Inhomogeneity within the tumor represents hemorrhage and infarction. (Courtesy of Steven A. Newman, MD.)

Parasellar meningiomas occur most often in middle-aged women. They frequently arise from the tuberculum sellae, planum sphenoidale, or anterior clinoid. Very commonly, they cause asymmetric bitemporal vision loss. Parasellar meningiomas may also enlarge and produce chiasmal compression during pregnancy.

Craniopharyngiomas are common in children but may present at any age, with a second incidence peak in adulthood. Often arising superiorly (ie, in the suprasellar or suprachiasmatic space), these tumors more frequently cause *inferior* bitemporal visual field loss.

Internal carotid artery aneurysms, particularly in the supraclinoid region, may produce a markedly asymmetric chiasmal syndrome, with optic nerve compression on the side of the aneurysm.

Therapy of parasellar tumors is complex and depends on the age of the patient; the nature, location, and extent of the tumor; its hormonal activity; and the severity of symptoms, particularly the presence of vision loss. Treatment modalities include

- observation only, if visual field is normal
- surgery (usually transsphenoidal, or craniectomy)
- medical therapy (primarily bromocriptine or cabergoline for prolactin-secreting pituitary tumors)
- radiation therapy (as either a primary or adjunctive therapy for incompletely resectable tumors)

After surgical resection of the tumor and relief of anterior visual pathway compression, vision recovery is usually rapid and may be dramatic, even in patients who experienced severe vision loss. Medical therapy for pituitary adenomas has a slower effect, taking days to weeks, but also shrinks the tumor and improves visual function in responsive cases. Prognosis is poor if mean RNFL thickness is less than 75 μm , as revealed on OCT scans (see Chapter 3, Fig 3-10). The ophthalmologist's role in the management of parasellar tumors is crucial, because vision loss may be the first sign of recurrence. Visual field, visual acuity, and color vision testing should be performed 2–3 months after treatment and at intervals of 6–12 months thereafter, depending on the course. Visual acuity and visual fields should be rechecked more often if the patient reports any ongoing change. Periodic neuroimaging is essential.

Delayed vision loss after therapy for parasellar lesions should prompt the following considerations:

- tumor recurrence
- delayed radionecrosis of the chiasm or optic nerves
- chiasmal distortion due to adhesions or secondary empty sella syndrome with descent and traction on the chiasm
- chiasmal compression from expansion of intraoperative overpacking of the sella with fat

Neuroimaging effectively helps differentiate among these entities and guides further management decisions.

Bresson D, Herman P, Polivka M, Froelich S. Sellar lesions/pathology. *Otolaryngol Clin North Am*. 2016;49(1):63–93.

Danesh-Meyer HV, Papchenko T, Savino PJ, Law A, Evans J, Gamble GD. In vivo retinal nerve fiber layer thickness measured by optical coherence tomography predicts visual recovery after surgery for parachiasmal tumors. *Invest Ophthalmol Vis Sci*. 2008;49(5):1879–1885.

Farrell CJ, Nyquist GG, Farag AA, Rosen MR, Evans JJ. Principles of pituitary surgery. *Otolaryngol Clin North Am*. 2016;49(1):95–106.

Fraser CL, Biousse V, Newman NJ. Visual outcomes after treatment of pituitary adenomas. *Neurosurg Clin N Am*. 2012;23(4):607–619.

Intrinsic lesions affecting the chiasm

Other, infrequent causes of chiasmal disorders include lesions such as infections (eg, tuberculosis, Lyme disease) and inflammation (eg, sarcoidosis, MS) (Fig 4-29). Neoplasms

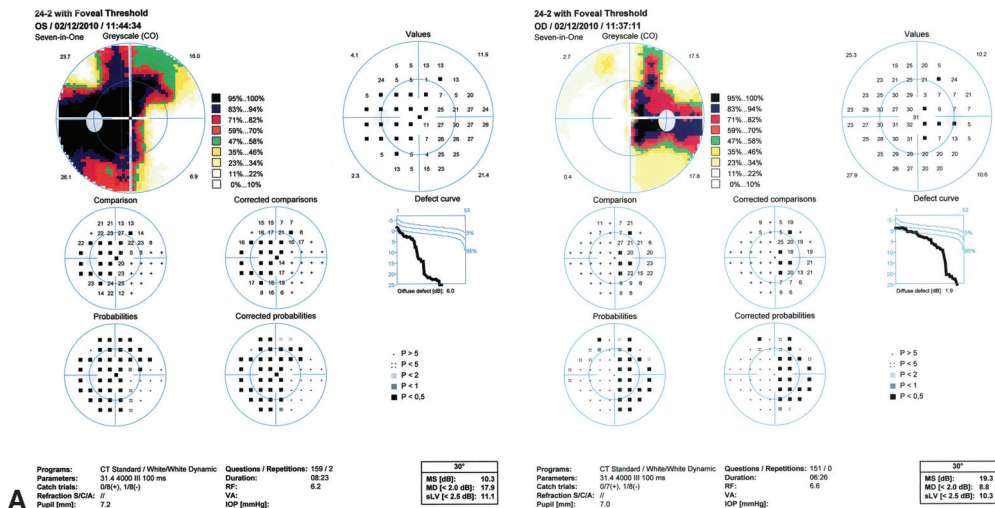


Figure 4-29 Chiasmal neuritis in a 36-year-old man with sudden-onset visual changes in both eyes. **A**, Visual field testing showed a “junctional scotoma” with a central visual field defect in the left eye (*left panel*) and temporal hemianopic defect in the right eye (*right panel*).

(Continued)

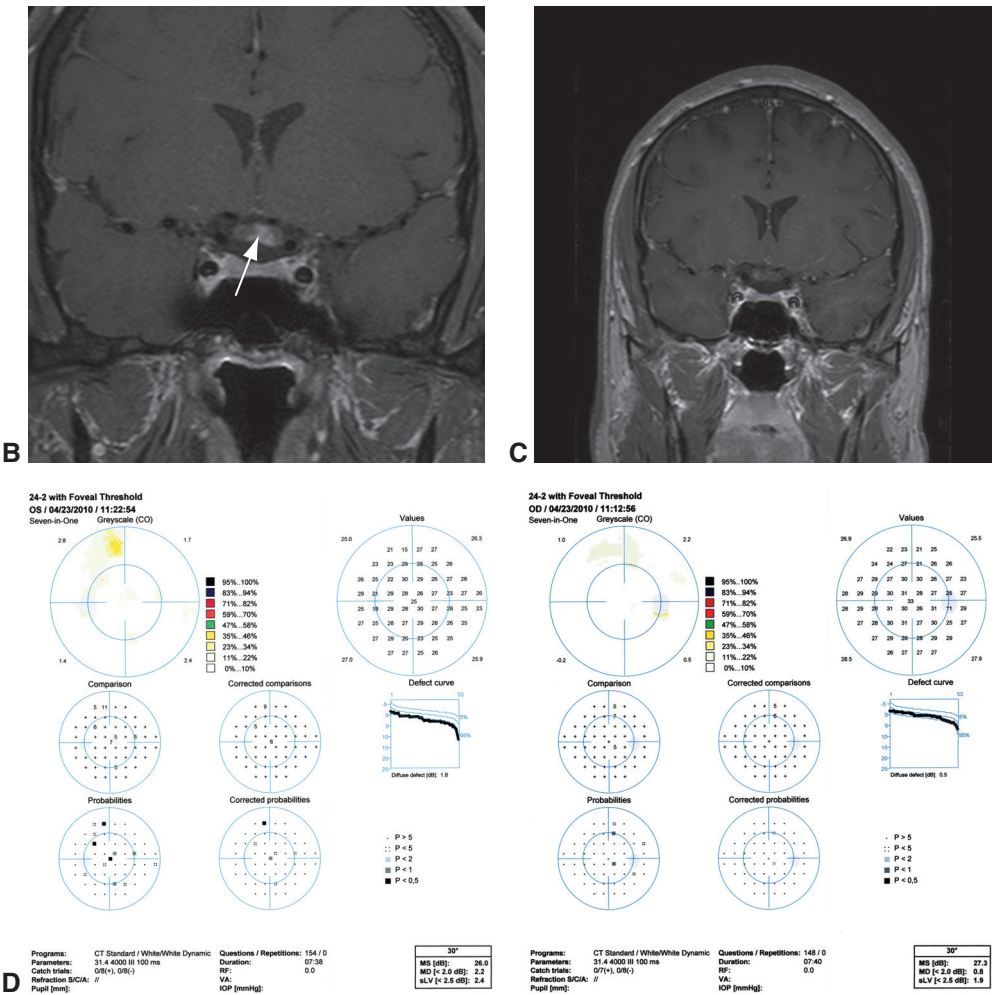


Figure 4-29 (continued) **B**, T1-weighted coronal, postgadolinium MRI scan shows enhancement (arrow) of predominantly the left side of the chiasm. **C**, Follow-up MRI scan shows resolution of the enhancement shown in **B**. **D**, Repeat visual field testing shows substantial improvement in both eyes. (Courtesy of Julie Falardeau, MD.)

can be either primary (eg, OPGs) or secondary (eg, metastasis). Significant closed-head trauma can injure the chiasm, causing a bitemporal hemianopia. Chiasmal injury may result from parasellar radiation therapy. Ischemia of the chiasm is very uncommon due to its robust collateral blood supply.

Retrochiasmal Lesions

As the fibers course through the retrochiasmal visual pathway (which consists of the optic tract; lateral geniculate body; and temporal, parietal, and occipital lobe visual radiations), crossed nasal fibers from the contralateral eye and uncrossed temporal fibers

from the ipsilateral eye come together (see Chapter 1). Retrochiasmal damage results in homonymous visual field defects that continue to respect the vertical midline. As fibers progress from the anterior to the posterior visual pathway, those from corresponding retinal regions of each eye tend to run more and more closely together. Lesions of the optic radiations classically produce dissimilar (*incongruous*) defects in the corresponding homonymous hemifields, whereas more posterior damage results in progressively similar (*congruous*) defects as lesions approach the occipital lobes. Although a highly congruous homonymous hemianopia might be expected to reflect occipital disease, the possibility of a more anterior lesion involving the optic tract or the lateral geniculate body cannot be excluded. Lesions severe enough to produce complete hemianopic defects may occur at any anteroposterior retrochiasmal location; such defects do not help localize lesions from the chiasm through the occipital cortex. Stroke is the most common cause of homonymous hemianopias, followed by traumatic brain injury and tumor.

Kedar S, Zhang X, Lynn MJ, Newman NJ, Bioussé V. Congruency in homonymous hemianopia. *Am J Ophthalmol.* 2007;143(5):772–780.

Zhang X, Kedar S, Lynn MJ, Newman NJ, Bioussé V. Homonymous hemianopias: clinical-anatomic correlations in 904 cases. *Neurology.* 2006;66(6):906–910.

Optic Tract

Lesions of the optic tract cause homonymous defects in the hemifields contralateral to the affected optic tract (see Fig 4-25). Damage to the optic tract frequently results from mass lesions such as aneurysms or tumors. These lesions may be associated with an ipsilateral RAPD if the optic nerve is also involved. Inflammatory and demyelinating lesions occasionally occur. Ischemic lesions of the tract are uncommon and result from infarction in the territory of the anterior choroidal artery. Because the fibers involved are primary neurons in the visual pathway (ie, retinal ganglion cells), the homonymous hemianopic visual field loss is accompanied by other findings that make up the *optic tract syndrome*:

- “Bow-tie” optic atrophy. Because the optic tract involves crossed fibers from the contralateral eye, the corresponding atrophy of crossed retinal fibers (those nasal to the macula) involves the papillomacular fibers and the nasal radiating fibers in the contralateral eye, causing atrophy in the corresponding nasal and temporal horizontal portions of the ONH (known as band or bow-tie atrophy) (see Chapter 1, Fig 1-18). Atrophy in the ipsilateral eye involves only the arcuate temporal bundles, which enter the ONH at the superior and inferior poles.
- *Mild RAPD in the contralateral eye.* This finding stems from the presence of greater sensitivity of the nasal retina than the temporal retina and the presence of more crossed than uncrossed pupillary fibers in the tract, causing more pupillary fibers from the contralateral eye to be damaged by a tract lesion.

Kardon R, Kawasaki A, Miller NR. Origin of the relative afferent pupillary defect in optic tract lesions. *Ophthalmology.* 2006;113(8):1345–1353.

Savino PJ, Paris M, Schatz NJ, Orr LS, Corbett JJ. Optic tract syndrome. A review of 21 patients. *Arch Ophthalmol.* 1978;96(4):656–663.

Lateral Geniculate Body

The lateral geniculate body (LGB) is a highly organized and layered retinotopic structure; therefore, lesions in this region can cause highly localized visual field defects. A congruous horizontal sectoranopia results from disruption within the vascular distribution of the posterolateral choroidal artery, a branch of the posterior cerebral artery. Loss of the upper and lower homonymous quadrants (also known as *quadruple sectoranopia*) with preservation of a horizontal wedge occurs with disruption of the anterior choroidal artery, a branch of the middle cerebral artery (Fig 4-30; see also Chapter 1, Fig 1-11). These visual field defects respect the vertical meridian, unlike the uncommon wedge defect observed in glaucoma. Sectoral optic atrophy occurs with LGB lesions, and in rare cases, bilateral LGB lesions cause blindness.

Luco C, Hoppe A, Schweitzer M, Vicuña X, Fantin A. Visual field defects in vascular lesions of the lateral geniculate body. *J Neurol Neurosurg Psychiatry*. 1992;55(1):12–15.

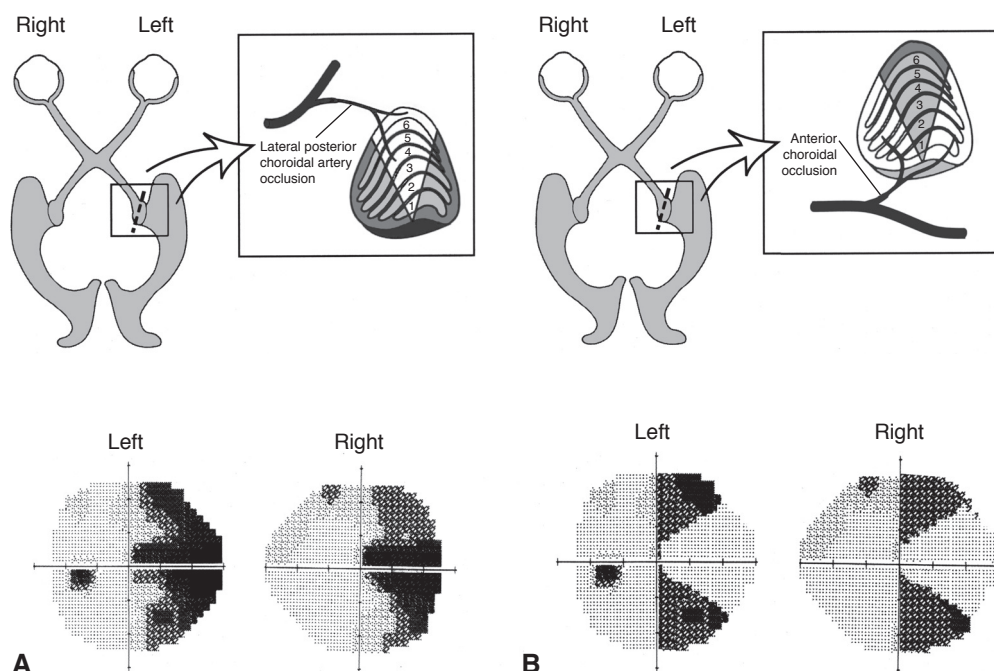


Figure 4-30 Visual field defects of the lateral geniculate body (LGB). Automated visual field testing shows **(A)** a central wedge-shaped homonymous sectoranopia caused by lateral posterior choroidal artery occlusion and **(B)** a loss of the upper and lower homonymous quadrants, with preservation of the horizontal wedge resulting from occlusion of the anterior choroidal artery. (Reproduced with permission from Trobe JD. *The Neurology of Vision*. Contemporary Neurology Series. Oxford: Oxford University Press, 2001:130.)

Temporal Lobe

Inferior visual fibers course from the LGB anteriorly in the *Meyer loop* of the temporal lobe (approximately 2.5 cm from the anterior tip of the temporal lobe). Superior fibers tend to course more directly posteriorly in the parietal lobe. Lesions affecting the Meyer loop thus produce superior, incongruous, homonymous defects contralateral to the lesion. These defects (so-called *pie in the sky* defects) spare fixation (Fig 4-31; see also Fig 4-25). Damage to the temporal lobe anterior to the Meyer loop does not cause visual field loss. Lesions affecting the radiations posterior to the loop produce homonymous hemianopic defects that extend inferiorly.

Tumors within the temporal lobe are a common cause of visual field loss (see Chapter 3). Neurologic findings of temporal lobe lesions include seizure activity, including olfactory seizures and formed visual hallucinations. Surgical excision of seizure foci in the temporal lobes may lead to visual field defects.

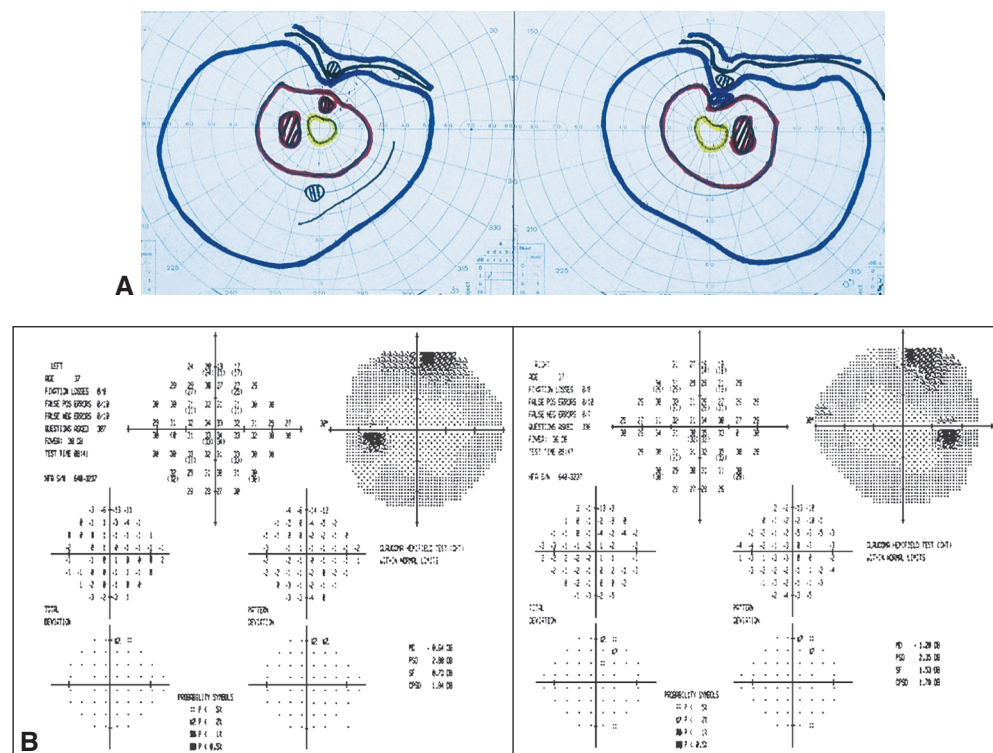


Figure 4-31 Visual field patterns after partial left temporal lobectomy for seizure disorder. **A**, Kinetic perimetry visual field results show a predominantly peripheral right superior homonymous quadrantanopia sparing fixation. **B**, Humphrey 30-2 perimetry testing detects a minimal portion of the field defects. (Courtesy of Steven A. Newman, MD.)

Parietal Lobe

Lesions of the parietal lobe, which often result from stroke or neoplasms, tend to involve superior fibers first, causing contralateral inferior homonymous hemianopic defects. More extensive lesions involve the superior visual fields but remain denser inferiorly. Parietal lobe syndromes encompass a wide variety of other neurologic effects, including perceptual problems (agnosia) and apraxia. Lesions of the dominant parietal lobe cause Gerstmann syndrome, a combination of acalculia, agraphia, finger agnosia, and left–right confusion. Lesions in the nondominant parietal lobe can cause contralateral neglect (see Chapter 6).

Damage to pursuit pathways that converge in the posterior parietal lobes (near the visual radiations) may cause abnormalities in optokinetic nystagmus (OKN). The examiner elicits the impaired OKN response by moving targets toward the lesion, inducing attempts to use the damaged pursuit pathway. Thus, a patient with a homonymous hemianopia due to a parietal lobe lesion will have a reduced OKN response with the target moving toward the affected side, whereas a patient with a homonymous hemianopia due to a lesion of the optic tract or occipital lobe will have an intact OKN response (see Chapter 8).

Occipital Lobe

As the fibers approach the occipital lobes, congruity becomes more important. Central fibers become separate from peripheral fibers; the central ones course to the occipital tip and the peripheral ones to the anteromedial cortex. Furthermore, there is cortical magnification of the area that corresponds to central vision in the posterior part of the striate cortex; the central 10° of visual field corresponds to approximately 50% of the visual cortex that extends from the posterior portion of the medial area to the occipital tip.

Because of the disparity in crossed versus uncrossed fibers, some of the peripheral nasal fibers leading to the anteromedial region are not matched with the corresponding uncrossed fibers. Therefore, the anteromedial region of the occipital lobe subserves a monocular “temporal crescent” of visual field in the far periphery (60°–90°). Finally, fibers localize within the occipital cortex superior and inferior to the calcarine fissure. Thus, visual field defects from occipital lobe lesions may have the following characteristics in the hemifields contralateral to the lesion:

- congruous homonymous hemianopia, possibly sparing the fixational region (Fig 4-32; see also Fig 4-25)
- monocular defect of the temporal crescent involving only the most anterior portion of the occipital lobe
- homonymous lesion sparing the temporal crescent in the eye contralateral to the lesion (Fig 4-33); kinetic perimetry testing is required
- homonymous quadrantanopia (superior or inferior) respecting the horizontal meridian

Most occipital lobe lesions encountered by ophthalmologists result from stroke (infarction in the territory of the posterior cerebral artery) and cause no neurologic deficits other than vision loss.

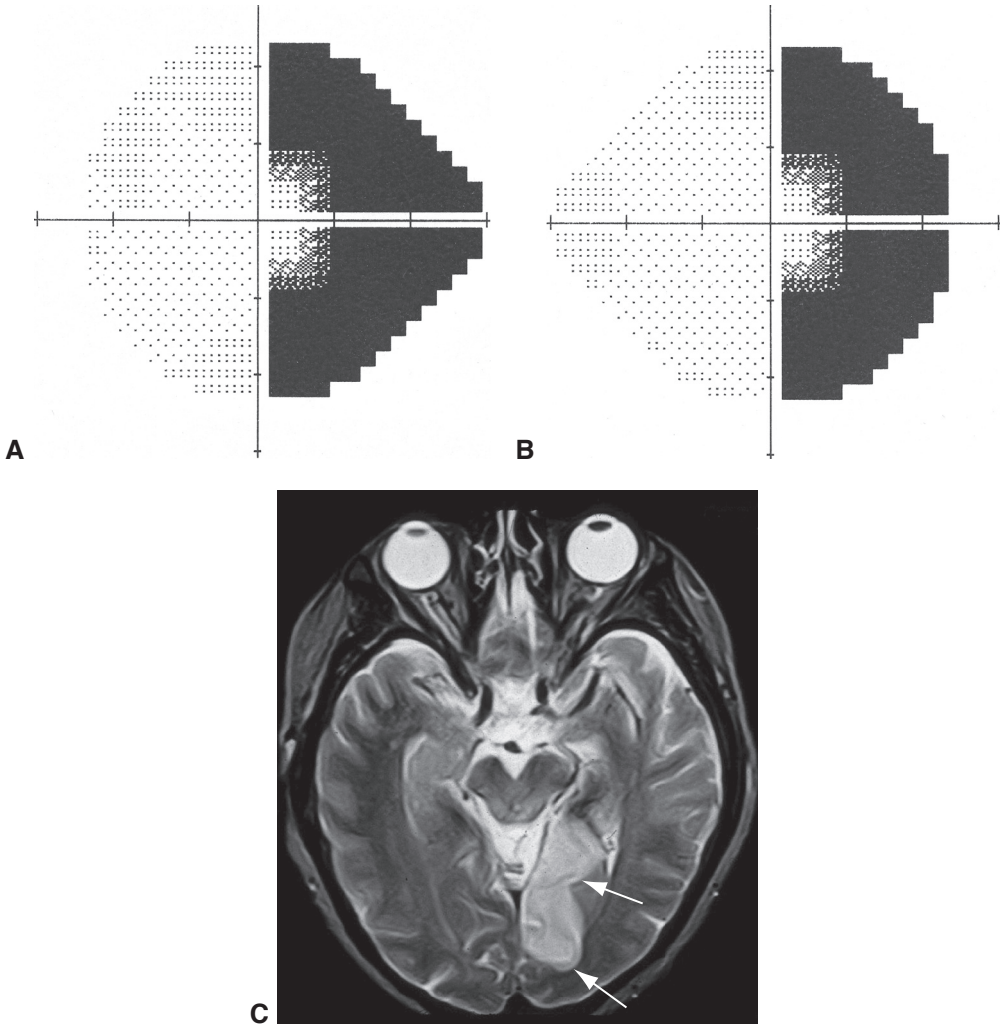


Figure 4-32 Occipital lobe infarction. **A, B**, Visual field patterns show congruous right homonymous hemianopia respecting the vertical meridian and sparing fixation. **C**, T2-weighted axial MRI scan showing left parieto-occipital stroke (arrows) sparing the occipital tip. (Parts A, B courtesy of Michael S. Lee, MD; part C courtesy of Steven A. Newman, MD.)

A *macula-sparing homonymous hemianopia* suggests a stroke involving the portion of the primary visual cortex supplied by the posterior cerebral artery. The tip of the occipital lobe receives a dual blood supply from the middle cerebral artery and the posterior cerebral artery. Occlusion of the posterior cerebral artery damages the primary visual cortex, except for the region representing the macula at the posterior tip of the occipital lobe, which remains perfused by the middle cerebral artery.

Systemic hypoperfusion often damages the occipital tip because the tip sits in a watershed area supplied by distal branches of the posterior and middle cerebral artery systems.

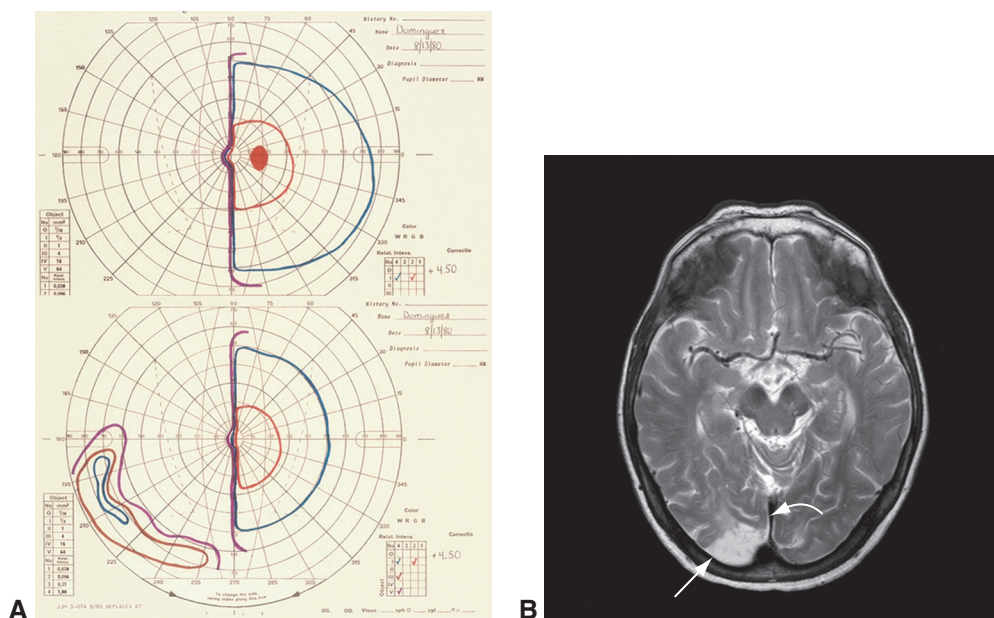


Figure 4-33 A 60-year-old woman presented with 3 episodes of transient visual loss to the left side. Her visual acuity was 20/20 bilaterally, but visual field patterns demonstrated a left homonymous hemianopia (**A**). Her temporal crescent was intact on the left side, and an MRI scan (**B**) confirmed the presence of a right occipital lobe stroke (*straight arrow*) compatible with an infarct and sparing of the anterior visual cortex (*curved arrow*). (Part A courtesy of Steven A. Newman, MD; part B courtesy of Sophia M. Chung, MD.)

This highly vulnerable region may be the only injured area, causing homonymous hemianopic scotomata (Fig 4-34).

Cerebral blindness results from bilateral occipital lobe damage. Normal pupillary responses and optic nerve appearance distinguish cerebral blindness from total blindness caused by lesions anterior to the LGB. Anton syndrome (denial of blindness), although classically associated with cortical blindness, can be due to a lesion at any level of the vision system severe enough to cause blindness. Bilateral occipital lobe lesions occasionally permit some residual visual function.

Disturbances of the primary visual cortex due to neoplasms, migraine, or drugs may also cause *unformed visual hallucinations*. *Formed hallucinations* (see Chapter 6) are usually attributed to lesions of the extrastriate cortex or temporal lobe. Patients with injury to the occipital cortex sometimes perceive moving targets but not static ones; this *Riddoch phenomenon* may also occur with lesions in other parts of the visual pathway. The Riddoch phenomenon probably stems from cells in the visual system responding better to moving stimuli than to those that are static.

Barton JJ. Higher cortical visual deficits. *Continuum (Minneap Minn)*. 2014;20(4 Neuro-ophthalmology):922–941.

Riddoch G. Dissociation of visual perceptions due to occipital injuries, with especial reference to appreciation of movement. *Brain*. 1917;40:15–57.

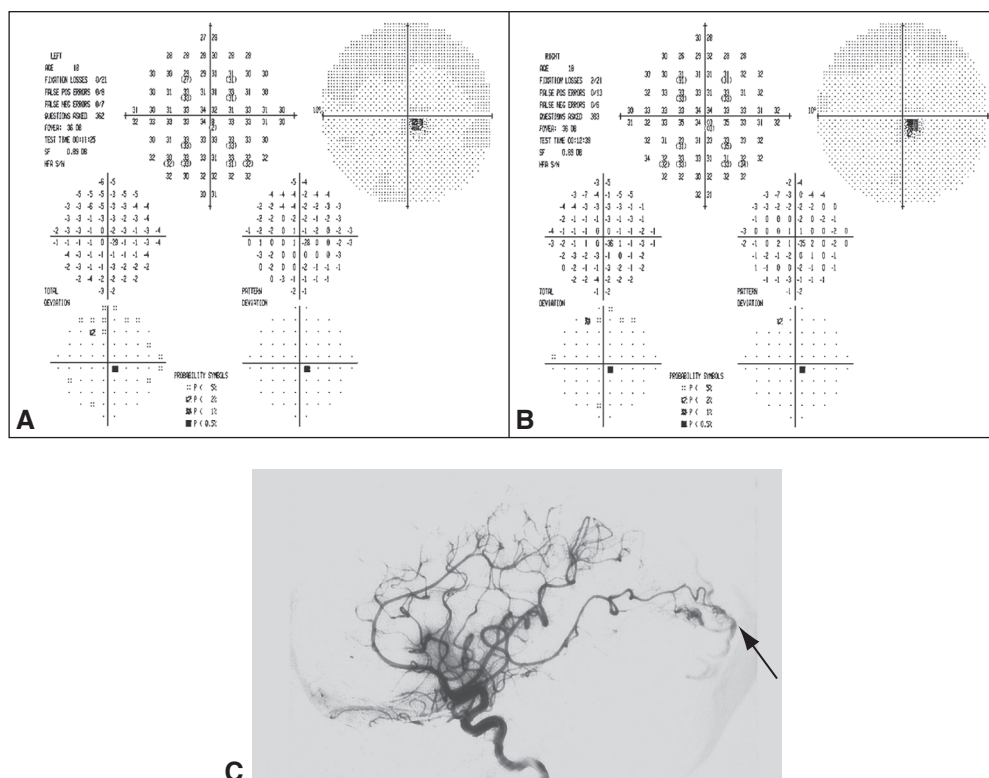


Figure 4-34 An 18-year-old woman presented with an 8-day history of sharp, left-sided headaches. Visual acuity was 20/20 bilaterally. **A, B,** She missed letters on the right of the chart, and bilateral 10-2 programs demonstrated a tiny 1° homonymous scotoma just below and to the right of fixation in both eyes. **C,** Her angiogram revealed an arteriovenous malformation involving the occipital tip (*arrow*). (Courtesy of Steven A. Newman, MD.)

Vision Rehabilitation

Ophthalmologists are encouraged to recognize the impact of vision loss on a patient's life and advise the patient of available vision rehabilitation options, including referral to a rehabilitation specialist. An evaluation at a low-vision clinic can be beneficial in terms of orientation and mobility and may offer the patient education about compensation techniques, such as computer training or use of prisms. Counseling regarding driving is also essential for patients with visual acuity loss or visual field defects. For additional information about vision rehabilitation, see BCSC Section 3, *Clinical Optics*.

American Academy of Ophthalmology Vision Rehabilitation Committee. Preferred Practice Pattern Guidelines. *Vision Rehabilitation*. San Francisco: American Academy of Ophthalmology; 2013. Available at: www.aao.org/ppp.

The Patient With Transient Visual Loss

Transient visual loss (TVL) is the sudden loss of visual function (partial or complete) in 1 or both eyes that lasts less than 24 hours. In general, the most important cause of transient monocular visual loss (TMVL) is retinal ischemia due to temporary occlusion of the central retinal artery or its branches. The most common cause of transient binocular visual disturbance is migraine. A systematic approach to the evaluation of patients with TVL is imperative, beginning with a detailed historical account of the visual loss that includes the following points:

- *Monocular versus binocular.* Establishing TVL as monocular or binocular is important for localizing the lesion; monocular loss implies a prechiasmal problem (anywhere from the cornea to the optic nerve), whereas binocular loss is a chiasmal or retrochiasmal (intracranial) problem. In rare instances, binocular TVL can reflect bilateral ocular disorders. Patients should be asked if they occluded each eye during the episode of visual loss. Clinicians should be aware that transient homonymous hemianopia is frequently misperceived as a monocular visual loss in the eye with the temporal field deficit.
- *Age.* In patients younger than 50 years, migraine is the most likely cause of binocular TVL. Arterial vasospasm can cause TMVL, but it is not common and is a diagnosis of exclusion. An important exception in pregnant women is eclampsia, in which TVL may be a harbinger of more serious and permanent visual loss, usually occurring within days of delivery (see Chapter 14). In older patients, cerebrovascular disease and giant cell arteritis (GCA) should be considered.
- *Duration of visual loss.* Monocular or binocular transient obscurations of vision lasting only seconds are often precipitated by a change in posture (eg, bending over) and are a common complaint in patients with optic nerve head (ONH) drusen or papilledema. Sudden TMVL lasting several minutes (typically no more than 15 minutes) is more suggestive of retinal ischemia from emboli. The duration of visual loss from retinal artery vasospasm varies; it may last seconds to 1 hour. TMVL resulting from ocular hypoperfusion or venous insufficiency can last up to 30 minutes. Occipital seizures are very brief binocular visual disturbances that last only a few seconds, whereas the binocular scintillating scotoma typical of migraine lasts 20–30 minutes.

- *Pattern/description of visual loss and recovery.* The classic description of TMVL from retinal emboli is a descending curtain in 1 eye; however, tunnel-like contraction of vision or sudden complete loss of vision may also occur. An altitudinal aspect of visual loss strongly suggests retinal emboli, but central retinal artery vasospasm can sometimes cause similar visual symptoms. Visual loss or disturbance precipitated by exercise can be caused by vasospasm, pigment dispersion syndrome, or demyelinating disease. *Uhthoff phenomenon* (transient visual blurring resulting from physical activity or elevation in body temperature) frequently occurs in patients with a current or previous episode of optic neuritis (see Chapter 4). Posterior circulation ischemia typically causes complete bilateral TVL (ie, cortical blindness) or a homonymous hemianopia, often in association with brainstem and/or cerebellar symptoms. Binocular visual disturbances with geometric quality (eg, “fortification” pattern) strongly suggest occipital lobe dysfunction (eg, migraine, ischemia, or seizure). Whiteout of vision in both eyes or gradual constriction (ie, “closing in”) of peripheral vision without positive visual phenomena may also signal occipital lobe ischemia.
- *Associated symptoms and additional signs.* Positive visual phenomena and headache accompanying binocular TVL suggest migraine. Persistent headaches and pulsatile tinnitus suggest increased intracranial pressure. In an elderly patient, TVL accompanied by headaches, weight loss, fever, malaise, jaw claudication, and scalp tenderness strongly suggests GCA. The presence of other neurologic symptoms and signs can help localize the vascular territory involved. Loss of consciousness, dizziness, diplopia, dysarthria, or focal weakness accompanying binocular TVL suggests cerebral ischemia in the posterior circulation (basilar artery territory). Focal weakness contralateral to the TMVL or aphasia suggests cerebral ischemia in the anterior circulation (internal carotid artery territory). Ipsilateral periorbital pain in the setting of an ipsilateral Horner syndrome may indicate an internal carotid artery dissection (see Chapter 10, Fig 10-4). TVL associated with exercise or change in position may suggest hypoperfusion (eg, ocular ischemic syndrome). Skin or joint changes or Raynaud phenomenon may accompany systemic vasculitis.
- *Predisposing conditions.* The examiner should conduct a careful interview, eliciting information about the presence of vascular risk factors such as atheromatous disease (carotid stenosis, coronary artery disease, peripheral arterial disease, aortic aneurysm), diabetes mellitus, hypertension, dyslipidemia, smoking, sleep apnea, cardiac source of emboli (previous myocardial infarction, valvulopathy, arrhythmia), intravenous drug use, family or personal history of a clotting disorder, systemic cancer, and history of connective tissue disease or vasculitis (eg, GCA or Takayasu arteritis).

Donders RC; Dutch TMB Study Group. Clinical features of transient monocular blindness and the likelihood of atherosclerotic lesions of the internal carotid artery. *J Neurol Neurosurg Psychiatry*. 2001;71(2):247–249.

Lawlor M, Perry R, Hunt BJ, Plant GT. Strokes and vision: the management of ischemic arterial disease affecting the retina and occipital lobe. *Surv Ophthalmol*. 2015;60(4):296–309.

Examination

Although the patient may report complete recovery of visual function, a thorough examination is crucial to rule out ocular and orbital causes of TVL, to assess the afferent visual function, and to look for retinovascular clues (eg, emboli, cotton-wool spots, vascular attenuation, or hemorrhage) that might suggest a specific diagnosis. This process should include testing for best-corrected visual acuity (also called corrected distance visual acuity), color vision, and intraocular pressure (IOP), as well as an examination of the pupils (testing for relative afferent pupillary defect or Horner syndrome), a slit-lamp examination, perimetry to look for residual visual field defects, and a dilated funduscopic examination. A positive photostress recovery test may indicate macular ischemia (see Chapter 3). When a vascular mechanism is suspected, retinal fluorescein angiography may be helpful.

Transient Monocular Visual Loss

Table 5-1 outlines the most common ocular, orbital, and systemic causes of TMVL.

Ocular Causes

Nonvascular ocular causes of TVL are very common and are usually excluded by an ocular examination.

Table 5-1 Causes of Transient Monocular Visual Loss

Ocular pathology (nonvascular causes)

- Tear-film abnormalities
- Epithelial basement membrane dystrophy
- Pigment dispersion
- Recurrent hyphema
- Intermittent angle-closure glaucoma
- Vitreous debris

Optic nerve disorders

- Acquired or congenital optic nerve head disease (eg, papilledema, drusen)
- Compressive lesions of the intraorbital optic nerve
- Demyelinating disease (Uhthoff phenomenon)

Vascular disease

- Embolic phenomenon
 - Carotid (atheroma, dissection)
 - Great vessels (aortic arch atheroma)
 - Cardiac source of emboli (valvulopathy, thrombus, arrhythmia)
- Vasculitis (eg, giant cell arteritis)
- Vasospasm
- Systemic hypotension
- Hyperviscosity/hypercoagulability states (eg, venous stasis or antiphospholipid antibody syndrome)
- Ocular hypoperfusion (eg, ocular ischemic syndrome)

Tear-film abnormalities often result in blurred vision that improves with blinking or a tear supplement. These abnormalities may also be associated with brief sharp or stabbing pain. Slit-lamp examination may reveal keratitis sicca. Dry eye can also provoke blepharospasm, which can lead to moments of visual loss (see Chapter 11, Fig 11-10).

Opacities, inflammation, or blood in the media of the anterior chamber or the vitreous can also cause episodic visual disturbance. For example, recurrent hyphema occasionally causes TMVL in patients with intraocular lenses who have uveitis-glaucoma-hyphema (UGH) syndrome. Release of pigment in the anterior chamber during exercise may occur in pigment dispersion syndrome.

Transient monocular visual obscurations that are accompanied by halos and pain should always prompt gonioscopy of the anterior chamber angle to assess for angle-closure glaucoma. The anterior lens should be inspected for glaukomflecken, which indicate prior episodes of angle-closure glaucoma.

TVL, prolonged visual recovery, or persistent afterimages following exposure to bright light suggests macular disorders, such as serous detachment, age-related macular degeneration, or ocular ischemia. In such patients, the photostress recovery test is often abnormal.

Patients with papilledema or congenital ONH anomalies (eg, drusen or anomalous optic nerve) experience grayouts or blackouts of vision (so-called transient visual obscurations). Such episodes are typically brief (less than 10 seconds) and often precipitated by changes in posture.

Kaiboriboon K, Piriyaawat P, Selhorst JB. Light-induced amaurosis fugax. *Am J Ophthalmol*. 2001;131(5):674–676.

Orbital Causes

TMVL that is specifically induced by moving the eyes toward a certain direction (gaze-evoked TMVL) suggests an orbital mass such as hemangioma or meningioma. The TMVL likely results from a combination of direct compression of the optic nerve and ischemia from positional vascular obstruction. Careful examination usually reveals other orbital findings, such as proptosis or limited ocular motility.

Otto CS, Coppit GL, Mazzoli RA, et al. Gaze-evoked amaurosis: a report of five cases. *Ophthalmology*. 2003;110(2):322–326.

Vascular Causes

After ocular and orbital causes of TMVL have been ruled out, vascular causes must be considered. The term “amaurosis fugax” refers specifically to a retinal transient ischemic attack (RTIA). Retinal arterial ischemia, whether transient or permanent, is a form of anterior circulation ischemic stroke caused by decreased blood flow in the ophthalmic branches of the internal carotid artery.

Vascular TMVL is a well-known prodromal syndrome of cerebral infarction. Vascular causes of TMVL are most often related to retinal emboli. However, TMVL may also result from optic nerve ischemia in patients with GCA or diffuse ocular hypoperfusion in patients with severe carotid artery disease, or it may precede central retinal vein occlusion.

Retinal emboli typically result in acute, painless visual loss in 1 eye, which is often described as a descending (or ascending) curtain over part or all of the visual field. The visual loss usually resolves over a few minutes. The examiner should conduct a careful interview and neurologic examination in order to look for contralateral neurologic symptoms and signs such as weakness and aphasia. Results of the ocular examination are often normal, although abnormalities of the retinal vasculature can occasionally be seen.

Emboli

Figure 5-1 shows the 3 most common types of emboli: cholesterol (Hollenhorst plaque), platelet-fibrin, and calcium. The characteristics of these emboli are reviewed in Table 5-2. Other less common varieties of emboli include those resulting from cardiac tumors (myxoma), fat (long-bone fractures, pancreatitis), sepsis, talc, air, silicone, and depot drugs (corticosteroids).

Atheroma formation occurs most commonly at the bifurcation of the common carotid artery into the internal and external carotid arteries and in the carotid siphon (Fig 5-2). Atheroma can remain stationary, become fibrotic, ulcerate, narrow and occlude the lumen, or release emboli. The internal carotid lumen must be reduced by 50%–90% before distal flow

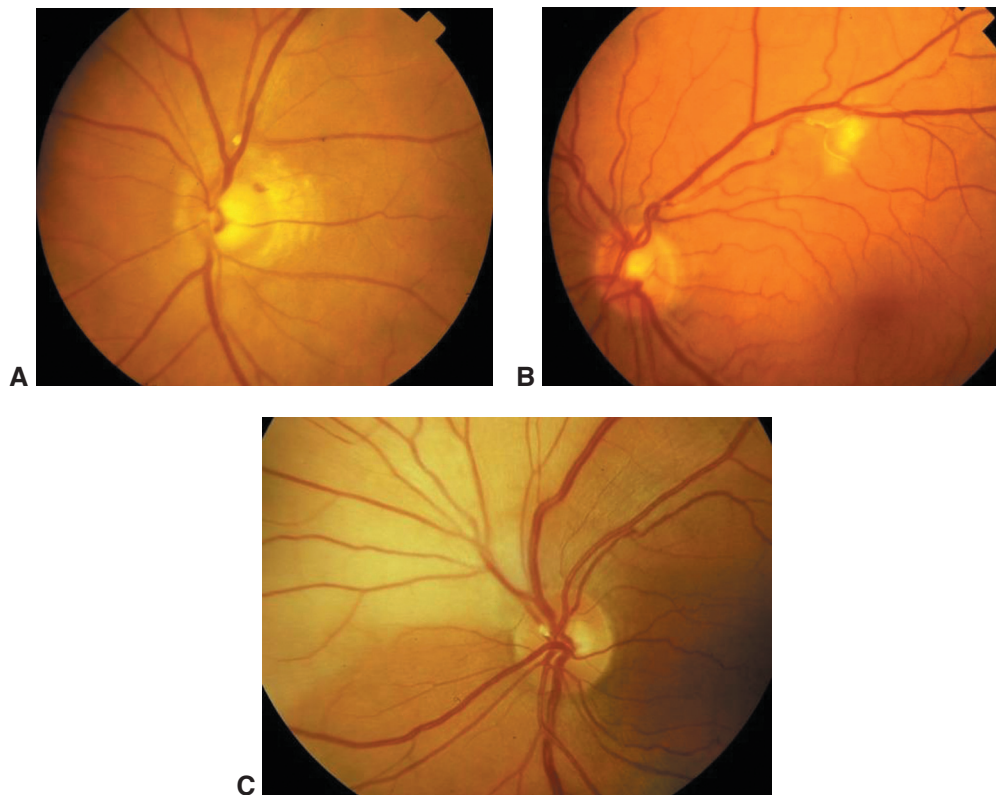


Figure 5-1 Common retinal emboli. **A**, Cholesterol embolus (Hollenhorst plaque) at the bifurcation of a retinal arteriole. **B**, Platelet-fibrin embolus. **C**, Calcific embolus with branch retinal artery occlusion. (Courtesy of Karl C. Golnik, MD.)

Table 5-2 Clinical Aspects of Common Retinal Emboli

Type	Appearance and Location	Source	Evaluation
Cholesterol (see Fig 5-1A)	Yellow-orange or copper color Refractile Globular or rectangular Usually located at major bifurcations	Usually common or internal carotid artery In rare instances, aorta or innominate artery	General medical evaluation* Noninvasive studies of carotid patency and aortic arch Cardiac assessment, including Holter monitoring and echocardiography
Platelet-fibrin (see Fig 5-1B)	Dull gray-white color Long, smooth shape Concave meniscus at each end Usually mobile; can lodge along course of vessel	Wall of atherosclerotic vessel Heart, especially valves	General medical evaluation* Noninvasive studies of carotid patency and aortic arch Cardiac assessment, including Holter monitoring and echocardiography Hematologic studies
Calcium (see Fig 5-1C)	Chalky white Large Round or ovoid Lodges in first or second bifurcation May overlie optic nerve head	Heart or great vessels, particularly as a result of rheumatic heart disease, calcific aortic stenosis, or calcification of mitral valve annulus	General medical evaluation* Noninvasive study of aortic arch Cardiac assessment, including echocardiography

*The evaluation is necessary not for determining the source of the embolus, but because these emboli are associated with an increased risk of cardiac disease and death.

is affected, but emboli may occur on ulcerated atheromatous plaques with any degree of stenosis. Emboli from aortic arch atheroma are also common. Treatable risk factors include hypertension, diabetes mellitus, hypercholesterolemia, and smoking. In younger patients with TMVL and periorbital pain or headache, a carotid dissection should be considered.

Cardiac emboli can arise from many causes, including cardiac arrhythmia, particularly atrial fibrillation, ventricular aneurysms, hypokinetic wall segments, endocarditis (infectious [associated with bacterial endocarditis] and noninfectious [marantic]), and valvular heart disease (including atrial myxoma).

Clinical and laboratory evaluation If an embolic cause of TMVL is suspected in a patient, a complete vascular and cardiac evaluation is urgently required; such patients have increased rates of morbidity and mortality from stroke, myocardial infarction, aortic aneurysm, and other related vascular events (see the following sections). Clinical examination should include assessment of the patient's pulse (in particular examining for atrial fibrillation), blood pressure, cardiac auscultation, and carotid artery auscultation (best done at the angle of the jaw, where the bifurcation is located). A carotid bruit indicates turbulent flow within the vessel, and it may be heard with narrowing of the external or internal carotid artery. However, a bruit will be absent if flow is undisturbed *or* if carotid occlusion is complete.



Figure 5-2 Magnetic resonance angiogram shows high-grade stenosis (*arrow*) of the cervical internal carotid artery at the bifurcation. (Courtesy of Aki Kawasaki, MD.)

Once GCA is ruled out (in patients older than 50 years), an immediate workup for a source of emboli must be initiated. Because RTIA may herald a devastating cerebral stroke, all patients with acute vascular TMVL should undergo a thorough vascular workup at once. It is best to immediately refer these patients to the nearest emergency department (preferably one affiliated with a stroke center). Sending a patient away for outpatient workup or to a primary care physician delays appropriate management.

It is important to obtain noninvasive vascular imaging of patients with TMVL urgently. The carotid arteries (in patients with TMVL), the vertebral arteries (in patients with binocular visual loss), and the aortic arch can reliably be evaluated by carotid ultrasonography (duplex scanning), magnetic resonance angiography (MRA), or computed tomographic arteriography (CTA). Ultrasonography, while it is a sensitive method of detecting cervical ulcerated plaques, has varying reliability. MRA and CTA results enable the visualization and characterization of the plaque in question, as well as of the surrounding arterial wall; they are also extremely useful for detecting internal carotid artery dissection.

Brain imaging performed to search for associated cerebral ischemia (ideally brain magnetic resonance imaging [MRI] with diffusion-weighted imaging [DWI]), should be obtained at the same time as the other tests for all patients with acute retinal ischemia, even those with TMVL. Results of studies have shown that up to 1 of every 4 patients with acute retinal ischemia has acute brain infarctions on DWI (often silent infarctions in patients who are neurologic asymptomatic). The probability of an abnormal MRI is higher in patients with embolic retinal ischemia (compared with patients with nonembolic retinal ischemia) and in patients with permanent visual loss (compared with patients with TVL). According to the 2013 guidelines from the American Heart Association (AHA), if the brain MRI shows acute cerebral ischemia, even if the patient is neurologically asymptomatic, the patient should be admitted to the hospital for a stroke and managed accordingly.

Echocardiography is useful for detecting valvular and cardiac wall defects, intracardiac tumors, and large thrombi. Transesophageal echocardiography, which is more sensitive than conventional transthoracic echocardiography, also allows evaluation of the aortic arch. A normal-appearing echocardiogram does not exclude the possibility of emboli because very small particles are not revealed. Prolonged inpatient cardiac monitoring or ambulatory Holter monitoring may document previously undetected cardiac arrhythmias. Suspected endocarditis should prompt blood culture testing.

If a cardiac or carotid source of embolism formation is not found, other systemic processes that could contribute to the stroke need to be considered. Major risk factors include advanced age, hypertension, ischemic heart disease, diabetes mellitus, hypercholesterolemia, smoking, and sleep apnea. Most of these conditions are treatable. Laboratory studies should be obtained to evaluate for these conditions and any others under clinical suspicion such as hypercoagulable states, collagen vascular diseases, vasculitis, or syphilis, depending on the presenting signs and symptoms of the patient.

Biousse V. Acute retinal arterial ischemia: an emergency often ignored. *Am J Ophthalmol.* 2014;157(6):1119–1121.

Biousse V, Trobe JD. Transient monocular visual loss. *Am J Ophthalmol.* 2005;140(4):717–721.

Jauch EC, Saver JL, Adams HP Jr, et al; American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Interdisciplinary Council on Peripheral Vascular Disease. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2013;44(3):870–947.

Prognosis and treatment Among patients with TMVL, significant carotid artery stenosis or occlusion is present in 53%–83% of cases. RTIA is a well-known prodromal syndrome of ischemic cerebral stroke; indeed, a transient ischemic attack (TIA) is a medical emergency associated with a high risk of early ischemic stroke and other cardiovascular events. Among patients with TIA (RTIA or hemispheric TIA [HTIA]), 10%–15% have a stroke within 90 days, with approximately half occurring within 48 hours. Individuals with TIA who survive the initial high-risk period have a 10-year stroke risk of approximately 19% and a combined 10-year risk of stroke, myocardial infarction, and vascular death of 43% (or approximately 4% per year). These statistics demonstrate the need for the urgent referral of patients with all types of TIA to an emergency department for expert evaluation and immediate treatment. As mentioned earlier, the most recent international guidelines from the AHA recommend that all patients with presumed retinal ischemia (whether transient or permanent) undergo urgent brain imaging and etiologic testing similar to patients with acute cerebral ischemia. According to these guidelines, an acute stroke is diagnosed in patients with abnormal DWI (these patients are then admitted to the hospital and managed accordingly), regardless of the patients' initial clinical presentation, whereas patients with normal MRI results usually are evaluated within 24 hours in a stroke clinic or an emergency department observation unit affiliated with a stroke center. Although the risk of stroke after an RTIA related to carotid atherosclerosis is lower than that after an HTIA, RTIAs must be managed similarly to HTIAs.

Several factors have been used to stratify the stroke risk in patients with RTIA, including male sex, age 75 years or older, previous history of HTIA or cerebral stroke, intermittent

leg claudication, stenosis of 80%–94%, and absence of collateral vessels on cerebral angiography. Patients with none or only 1 of these risk factors have a 3-year ipsilateral stroke risk of 1.8%. However, for patients with 2 risk factors, the stroke risk is 12.3%, and for patients with 3 or more risk factors, the stroke risk increases to 24.2%. Thus, surgical management of carotid atheromatous stenosis (eg, carotid endarterectomy) may be more beneficial for those patients who have RTIA and 3 or more of these risk factors.

Medical treatment of RTIA due to carotid artery stenosis begins with antiplatelet agents (aspirin, aspirin-dipyridamole, or clopidogrel). Treating the vascular risk factors and employing other secondary prevention measures (eg, carotid endarterectomy, treating arrhythmia, treating cardiac sources of emboli) is essential; treatment should be initiated as soon as possible by a stroke neurologist.

Benavente O, Eliasziw M, Streifler JY, Fox AJ, Barnett HJ, Meldrum H; North American Symptomatic Carotid Endarterectomy Trial Collaborators. Prognosis after transient monocular blindness associated with carotid-artery stenosis. *N Engl J Med*. 2001;345(15):1084–1090.

Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009;40(6):2276–2293.

Helenius J, Arsava EM, Goldstein JN, et al. Concurrent acute brain infarcts in patients with monocular visual loss. *Ann Neurol*. 2012;72(2):286–293.

Lauda F, Neugebauer H, Reiber L, Jüttler E. Acute silent brain infarction in monocular visual loss of ischemic origin. *Cerebrovasc Dis*. 2015;40(3–4):151–156.

Lee J, Kim SW, Lee SC, Kwon OW, Kim YD, Byeon SH. Co-occurrence of acute retinal artery occlusion and acute ischemic stroke: diffusion-weighted magnetic resonance imaging study. *Am J Ophthalmol*. 2014;157(6):1231–1238.

Additional systemic causes

Other possible systemic causes of vascular TMVL are ophthalmic artery disease, vasculitis (including GCA), hyperviscosity syndrome, antiphospholipid antibody syndrome, and central retinal artery vasospasm.

Vasculitis TMVL in older patients (usually older than 50 years) can be caused by GCA and may signal impending acute and permanent visual loss in 1 or both eyes. Therefore, a directed history of older patients with monocular or binocular TVL should include inquiries about the following symptoms:

- headache
- scalp tenderness
- jaw claudication
- weight loss
- proximal joint pain
- muscle aches
- malaise

However, systemic symptoms of GCA are absent in up to 20% of patients with visual symptoms (so-called “occult GCA”). Erythrocyte sedimentation rate, C-reactive protein concentration, and platelet count should be assessed in all patients aged 50 years or more who present with TVL (see Chapter 14). If GCA is the suspected cause of TVL, immediate treatment with high-dose corticosteroids is the only way to prevent progression to permanent visual loss.

Hayreh SS, Podhajsky PA, Zimmerman B. Occult giant cell arteritis: ocular manifestations. *Am J Ophthalmol*. 1998;125(4):521–526.

Ocular hypoperfusion Ocular hypoperfusion may lead to TMVL in 3 classic scenarios:

1. *Central retinal vein occlusion (CRVO)*. Patients with CRVO may report TVL that lasts seconds to minutes, with full recovery to normal vision afterward. Such symptoms may predate more lasting visual loss by days or weeks, or the symptoms may cease when collateral vessels develop.
2. *Change in posture from a sitting to a standing position*. In these patients, the TMVL is usually related to severe stenosis of the great vessels, or GCA. The patient may note progressive restriction of vision from the periphery (“diaphragm pattern”) that lasts from seconds to 1–2 minutes.
3. *Ocular ischemic syndrome (OIS)*. This syndrome is characterized in part by a hypotensive, ischemic retinopathy with low retinal artery pressure, poor perfusion, midperipheral dot-and-blot retinal hemorrhages, and dilated (nontortuous) veins (*venous stasis retinopathy*). Recurrent orbital pain that improves when the patient lies down is highly suggestive of carotid occlusive disease. In the early stages, patients may experience transient or persistent blurred vision or TMVL on exposure to bright light. Severe ocular ischemia causes anterior segment changes that may be confused with chronic intraocular inflammation. The patient may have decreased vision; a red, painful eye with episcleral vascular injection; and aqueous flare (ischemic uveitis). Even though neovascularization of the chamber angle and iris is common, IOP may be low, normal, or high. In this instance, low or normal IOP is the result of impaired ciliary body perfusion. Fundus changes may include dilated retinal veins, narrowed retinal arteries with microaneurysms, midperipheral dot-and-blot hemorrhages, and macular edema (Fig 5-3). Treatment of OIS is challenging and includes ocular reperfusion (via carotid endarterectomy, or carotid stenting when possible), IOP-lowering drugs, and treatment for neovascularization, including panretinal photocoagulation. If the preoperative IOP is low, restoration of blood flow may precipitate dangerously high IOP. Once the patient incurs signs of chronic hypoperfusion, however, improvement is unlikely. In other patients, carotid occlusion may be too advanced for surgical correction. Early detection is crucial because neovascularization and progressive ocular ischemia result from prolonged hypoperfusion (see also BCSC Section 12, *Retina and Vitreous*).

Mendrinis E, Machinis TG, Pournaras CJ. Ocular ischemic syndrome. *Surv Ophthalmol*. 2010;55(1):2–34.

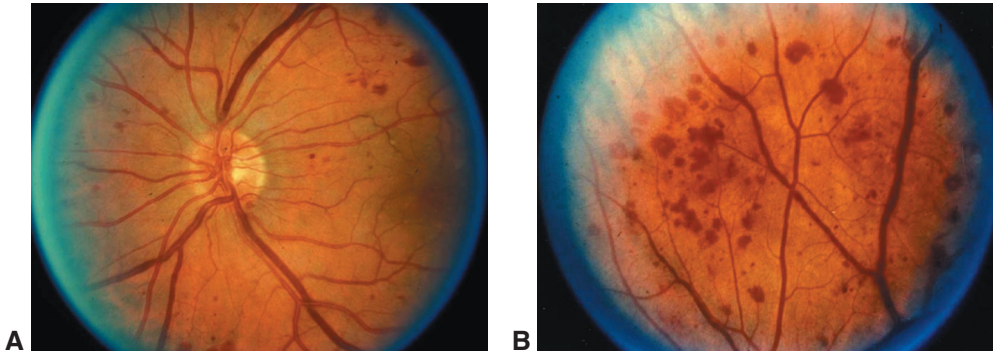


Figure 5-3 Ocular ischemic syndrome. **A**, Fundus demonstrates retinal venous dilation and scattered hemorrhages. **B**, Midperipheral dot-and-blot hemorrhages. (Reprinted with permission from John E. Carter, MD. From Carter JE. Panretinal photocoagulation for progressive ocular neovascularization secondary to occlusion of the common carotid artery. *Ann Ophthalmol.* 1984;16(6):572–576.)

Vasospasm, hyperviscosity, and hypercoagulability TMVL can result from vasospasm of the retinal artery. Patients are generally young and experience stereotypic episodes of painless severe TMVL. The vision returns to normal in between episodes, and the prognosis is usually good. The ocular examination findings are usually normal, but occasionally, when the patient is seen during the episode of visual loss, funduscopic examination reveals constriction of the retinal arteries. The diagnosis of vasospastic TMVL is one of exclusion. Before a diagnosis of vasospastic TMVL is made, the workup should rule out all causes of embolic retinal TIA. If the patient is older than 50 years, tests for erythrocyte sedimentation rate and C-reactive protein concentration should be obtained to rule out GCA. Particularly in younger patients, hyperviscosity syndrome and hypercoagulable states (eg, antiphospholipid syndrome, thrombocytosis, or other thrombophilia disorders) should be considered.

Hyperviscosity is a rare cause of TVL. Approximately 10% of patients with polycythemia vera report episodes of TMVL.

Winterkorn JMS, Burde RM. Vasospasm—not migraine—in the anterior visual pathway. *Ophthalmol Clin North Am.* 1996;9:393–405.

Binocular Transient Visual Loss

Common causes of binocular TVL include

- migraine
- occipital mass lesions: tumor, arteriovenous malformation
- occipital ischemia (TIA): embolic, vasculitic, hypoperfusion
- occipital seizures

Migraine

The most common cause of binocular TVL is the homonymous hemianopic defect caused by migrainous visual aura. The patient typically notes a small scotoma in homonymous

portions of the visual field, surrounded by jagged, luminous, shimmering edges. The scotoma enlarges over several minutes, sometimes to a complete homonymous hemianopia, then gradually disappears. The vision typically returns to normal within 20–30 minutes (the aura may be as short as 5 minutes; it is always less than 1 hour). The visual aura is usually followed by a headache, although some patients may experience the typical aura without headache (previously termed acephalgic migraine). The patient's vision is completely normal between episodes, and the visual phenomena typically change sides. Evaluation of migraine is discussed in Chapter 12.

Occipital Mass Lesions

In a patient with episodic headaches and binocular TVL, if the attacks always occur on the same side, a structural lesion—usually an occipital arteriovenous malformation or tumor—must be ruled out. Such patients require contrast-enhanced brain MRI and/or MRA.

Occipital Ischemia

Episodes of complete binocular TVL may represent a TIA that involves the occipital lobes in the distribution of the basilar artery or the posterior cerebral arteries (see Chapter 1); these episodes are particularly common in older patients with vascular risk factors or cardiac anomalies. As opposed to migraine, hemianopic events of ischemic origin are typically sudden in onset and last only a few minutes. There may be an associated headache, especially in the brow contralateral to the hemianopia, but the pain occurs at the time of TVL. Nonophthalmic symptoms of TIAs in the vertebrobasilar system are discussed in Chapter 14.

Patients with suspected occipital TIA must be referred immediately to an emergency department and evaluated by a neurologist.

Lawlor M, Perry R, Hunt BJ, Plant GT. Strokes and vision: the management of ischemic arterial disease affecting the retina and occipital lobe. *Surv Ophthalmol.* 2015;60(4):296–309.

Occipital Seizures

Occipital seizures typically produce unformed positive visual phenomena, such as colored or swirling lights or a whiting out of vision, like “bubbles” or “a flashbulb going off.” However, some patients experience negative visual symptoms, typically described as a blacking out of vision. These episodes usually last a few seconds to minutes, although they may persist for many hours (status epilepticus amauroticus). Most adults with occipital seizures harbor a structural lesion (eg, tumor, arteriovenous malformation, or trauma); in children, such seizures are more often benign. A normal electroencephalogram does not rule out seizures; prolonged electroencephalogram monitoring may be required. The visual symptoms resolve with anticonvulsant therapy.

Kun Lee S, Young Lee S, Kim DW, Soo Lee D, Chung CK. Occipital lobe epilepsy: clinical characteristics, surgical outcome, and role of diagnostic modalities. *Epilepsia.* 2005;46(5):688–695.

The Patient With Illusions, Hallucinations, and Disorders of Higher Cortical Function

Patients are often reluctant to report “seeing things” due to concerns that it may reflect mental illness; however, many visual hallucinations or illusions are not a harbinger of psychiatric disease but are instead indicators of brain, ocular, or optic nerve pathology. The ophthalmologist should therefore make sure to ask patients about these symptoms. *Illusions* are false perceptions of visual stimuli. For example, a person looking at stationary high-contrast borders may perceive an illusion of movement. A *hallucination* is the subjective perception of an object or event when no sensory stimulus is present. Illusions should disappear with eye closure; hallucinations often do not.

When assessing a patient who reports illusions or hallucinations, the first step is to ascertain the patient’s mental status and the function of the patient’s afferent visual system. Patients with dementia or altered sensorium (eg, delirium, hypnosis) are prone to hallucinations. Reduced visual acuity or visual field loss often leads to positive visual phenomena. The ophthalmologist should determine the corrected distance visual acuity, assess color vision, and test for perimetry. By localizing the disorder anatomically, the ophthalmologist is able to establish a likely pathophysiology, or at least a differential diagnosis.

Celesia GG. The mystery of photopsias, visual hallucinations, and distortions. *Suppl Clin Neurophysiol*. 2006;59:97–103.

Winterkorn JM, Fraser CE, Nirenberg MJ. Ophthalmic features of neurodegenerative diseases. *Focal Points: Clinical Modules for Ophthalmologists*. San Francisco: American Academy of Ophthalmology; 2010, module 1.

The Patient With Visual Illusions and Distortions

The alterations of perception that make up the spectrum of illusions can arise at various points in the visual system. Nonvisual causes of illusions and hallucinations are listed in Table 6-1.

Fraunfelder FT, Fraunfelder FW, Chambers WA. *Drug-Induced Ocular Side Effects*. 7th ed. Philadelphia: Saunders/Elsevier; 2014.

Table 6-1 Nonvisual Causes of Illusions and Hallucinations**Neurological conditions**

Alzheimer disease, epilepsy, Huntington chorea, Lewy body dementia, narcolepsy, Parkinson disease

Medications and hallucinogens

Anticholinergic and dopaminergic drugs, cephalosporins, psychotropic and antiseizure medications, sulfa drugs, vasoconstrictors, vasodilators
 Clomiphene, cyclosporine, indomethacin, digoxin, lidocaine, lithium, nefazodone, sildenafil, topiramate, trazodone, zonisamide
 Amphetamines, cocaine, lysergic acid diethylamide (LSD), mescaline, psilocybin
 Atropine, homatropine, topical scopolamine

Psychiatric conditions

Affective disorders, conversion disorders, schizophrenia

Toxic and metabolic conditions

Alcohol withdrawal (delirium tremens)
 Hepatic disease, infection (fever), uremia

Miscellaneous

Intense emotional experiences
 Hypnosis, sensory deprivation, sleep deprivation

Ocular Origin

Many illusions have an ocular basis and may be classified as optical or retinal (due to alterations in photochemical transduction).

Optical causes

Irregularities in the eye's refracting elements can produce visual distortion and resulting illusions such as ghost images (monocular diplopia), movement, or multiple images. Any alteration in the tear film (eg, dry eye syndrome) or in the corneal surface (eg, keratoconus, corneal edema, or scarring) can distort vision. Peripheral iridectomy may result in dysphotopsia and shadowing of images. Early cataract may produce visual distortion rather than decreased visual acuity, especially in eyes with early oil-droplet nuclear sclerotic changes or posterior subcapsular changes. The crystalline lens acts as a filter, changing the transmitted spectrum of light, and thereby producing altered perception of shape and color. Cataract extraction may also produce changes in brightness and color perception. After intraocular lens implantation, some patients experience temporal field visual disturbances such as an arc of light or a dark area, termed *positive* or *negative dysphotopsia*, respectively; these disturbances are typically transient and resolve spontaneously.

Retinal causes

Any disruption of normal foveal architecture (eg, epiretinal membrane, macular edema, macular hole, or subretinal disease) can cause visual distortion. Changes in the position of the retinal photoreceptors can cause various alterations in vision.

Metamorphopsia (perceptual distortion) is characteristic of macular disorders. Patients with these disorders usually report that linear objects appear curved or discontinuous. In patients with intraretinal edema, the retinal elements are often pushed apart,

causing micropsia (perceived image shrinkage). Macropsia (perceived image enlargement) is much rarer and can occur if the photoreceptors are pushed together.

The retina may be the source of changes in color perception (dyschromatopsia) associated with drug effects (eg, digoxin-induced yellowing of vision, sildenafil-induced blue tinge). Other changes in color perception may be related to vitamin A deficiency and choroidal or retinal ischemia, which can also lead to persistent afterimages or dazzle (brightness that temporarily confuses vision).

Optic Nerve Origin

After an episode of demyelinating optic neuritis, a relative conduction delay within the affected optic nerve may lead to an altered perception of motion. Because of the disparity in neuronal transmission, a pendulum, for example, may appear to trace an elliptical path instead of its true single-plane oscillation (*Pulfrich phenomenon*).

Cortical Origin

Depending on the affected area (the primary visual cortex [V1] or the associative areas V2, V3, and V4), occipital lobe pathology may alter the perceived shape and position of an object, change perception of motion, cause color vision loss, or induce multiplicity of images. Patients with parietal lobe abnormalities commonly experience disorders of visual perception, such as micropsia, macropsia, *teleopsia* (objects appearing too distant), and *pelopsia* (objects appearing too close). See Chapter 1 for anatomy discussion.

The Patient With Hallucinations

Hallucinations are perceptions unrelated to active stimuli. They may originate anywhere along the visual pathway but occur most commonly within the globe or cortex. Hallucinations may be *formed* (eg, real objects such as animals, flowers, cars, or people) or *unformed* (eg, light, spots, dots, or geometric patterns).

Ocular Origin

Unlike illusions, hallucinations have no optical causes. Vitreous detachment with persistent vitreoretinal adhesions may produce photopsias (flashing lights) or vertical white flashes (so-called lightning streaks of Moore). Such hallucinations are often apparent in a dark environment and may be induced by saccades. Retinal detachment may produce persistent photopsias and floaters.

Photopsias resulting from outer retinal diseases are often continuous. They may be simple white lights or form geometric webs that take on colors, including silver and gold. Photopsias often herald the onset of autoimmune retinopathy, including cancer-associated retinopathy, a paraneoplastic process. In addition, photopsia may accompany a variety of retinal, retinal pigment epithelium, and choroidal abnormalities (eg, multiple evanescent white dot syndrome, acute zonal occult outer retinopathy, or birdshot chorioretinopathy; see BCSC Section 12, *Retina and Vitreous*, for more on these conditions).

Gass JD, Agarwal A, Scott IU. Acute zonal occult outer retinopathy: a long-term follow-up study. *Am J Ophthalmol*. 2002;134(3):329–339.

Gordon LK. Paraneoplastic syndromes in neuro-ophthalmology. *J Neuroophthalmol*. 2015; 35(3):306–314.

Zaret BS. Lightning streaks of Moore: a cause of recurrent stereotypic visual disturbance. *Neurology*. 1985;35(7):1078–1081.

Optic Nerve Origin

Optic neuritis often produces phosphenes induced by eye movement or a dark setting. Patients with subacute or long-standing optic neuropathy may experience *sound-induced photisms* (sensations of color or light induced by a loud noise). These photisms are attributed to discharges from the lateral geniculate nucleus, which is also responsive to sound.

Jacobs L, Karpik A, Bozian D, Gøthgen S. Auditory-visual synesthesia: sound-induced photisms. *Arch Neurol*. 1981;38(4):211–216.

Cortical Origin

Although the conventional teaching is that lesions affecting the anterior optic radiations (ie, temporal lobe) typically cause formed hallucinations while more posterior lesions (ie, parietal and occipital lobes) typically produce unformed hallucinations, there are many exceptions. In rare cases, lesions involving the mesencephalon may cause formed hallucinations (peduncular hallucinosis) that can be constant; they are usually associated with an inverted sleep-wake cycle. Associated symptoms may occur if adjacent midbrain structures are involved.

Palinopsia

Interesting cortical phenomena may occur with disorders of both the dominant and, more frequently, the nondominant temporal, parietal, and occipital lobes. Palinopsia is visual perseveration after removal of the original stimulus (multiple afterimages) and can be divided into two categories: illusory and hallucinatory. Illusory palinopsia is triggered by contrast and/or motion; the visual afterimage or trails appear in the same location as the original stimulus. Migraine, hallucinogenic drugs such as lysergic acid diethylamide (LSD), and medications (eg, clomiphen, nefazodone, topiramate, trazodone, and zonisamide) can cause illusory palinopsia. In contrast, hallucinatory palinopsia is not affected by environmental conditions, and the perseverated image can occur in a different location than the original stimulus. When the afterimages are associated with homonymous hemianopia and appear in the blind hemifield, a posterior cortical lesion is usually present.

Gersztenkorn D, Lee AG. Palinopsia revamped: a systematic review of the literature. *Surv Ophthalmol*. 2015;60(1):1–35.

Yun SH, Lavin PJ, Schatz MP, Lesser RL. Topiramate-induced palinopsia: a case series and review of the literature. *J Neuroophthalmol*. 2015;35(2):148–151.

Temporal, parietal, and occipital lobe lesions

Temporal lobe lesions most often produce olfactory and gustatory hallucinations; however, they can also cause complex, formed hallucinations in either the ipsilateral or the

contralateral visual field. Epilepsy is the most common cause of hallucinations from this region. An accompanying visual aura implies that the seizure began focally.

In the parietal lobe, hallucinations may be either formed or unformed, whereas occipital lobe disorders commonly cause unformed hallucinations. Patients with occipital lobe lesions may describe white or colored flashes of light, kaleidoscopic colors, moving discs, flickering, or a hexagonal array (eg, chicken-wire or honeycomb patterns). A complete whiteout of vision suggests bilateral occipital lobe ischemia.

Hallucinations within a homonymous hemianopia or quadrantanopia are generally complex; they may be static or move throughout the visual field.

Celesia GG. Positive spontaneous visual phenomena. In: Celesia GG, ed. *Disorders of Visual Processing*. Edinburgh: Elsevier; 2005:353–370. *Handbook of Clinical Neurophysiology*; vol 5.

Migraine

Abnormal excitatory activity in the cerebral cortex, followed by a wave of depressed neuronal function (*cortical spreading depression*), is believed to cause the visual phenomena of migraine. In migraine with aura, the binocular hemifield visual phenomena can last 5–60 minutes and are always followed by a headache (see Chapter 12). In addition to the classic fortification spectra (teichopsia), false sensation of motion (scintillations), and false perception of colors, patients may also experience “Alice in Wonderland effect” (micropsia and/or macropsia), formed or unformed images, or visual distortion. Common patient descriptions of visual phenomena experienced during a migraine with aura include heat waves, cracked glass, kaleidoscopic vision, or fragmented vision. Patients may also experience *typical aura without headache*, previously termed *acephalgic migraine*.

Persistent positive visual phenomena

These visual phenomena are often described as snow, television static, dots (black-and-white or colored), colored pixelated images, or a rainlike pattern affecting the entire visual field. Such visual phenomena usually last for months to years and, while bothersome, rarely interfere with visual function. They are commonly, but not exclusively, noted in patients with a personal or family history of migraine. Prophylactic treatment with migraine medication is usually unsuccessful. Persistent positive visual phenomena are distinct from migraine aura and cannot be attributed to another disorder. Isolated visual snow (with no other neurological or visual symptoms) may be a normal phenomenon.

Schankin CJ, Maniyar FH, Digre KB, Goadsby PJ. ‘Visual snow’—a disorder distinct from persistent migraine aura. *Brain*. 2014;137(Pt 5):1419–1428.

Sleep-associated visual hallucinations

Hypnagogic hallucinations are vivid perceptual experiences that occur at sleep onset, whereas hypnopompic hallucinations are similar experiences that occur during awakening. Both phenomena are frequently associated with sleep disorders (eg, insomnia and daytime sleepiness) and may be suggestive of narcolepsy.

Charles Bonnet syndrome

Visually impaired patients with preserved cognitive status may experience visual hallucinations, a condition known as *Charles Bonnet syndrome*. Patients may have formed or

unformed hallucinations that are either persistent or abruptly intermittent. Hallucinations may be elementary or highly organized and complex. Patients with this syndrome have a clear sensorium and realize the hallucinations are not real. If the cause of the vision loss is known and there is no homonymous visual field defect, neuroimaging is unnecessary. Common underlying conditions include age-related macular degeneration, glaucoma, diabetic retinopathy, and cerebral infarction. Medical treatment is often unsuccessful in suppressing the hallucinations.

Menon GJ, Rahman I, Menon SJ, Dutton GN. Complex visual hallucinations in the visually impaired: the Charles Bonnet syndrome. *Surv Ophthalmol*. 2003;48(1):58–72.

The Patient With Disorders of Higher Cortical Function

The process of “seeing” begins when visual information reaches the occipital striate cortex (area V1). For visual awareness to occur, this information must be processed by the associative cortical areas (see Chapter 1). Visual information is then projected through a ventral occipitotemporal pathway and a dorsal occipitoparietal pathway (see Chapter 1, Fig 1-22). The ventral pathway helps process the physical attributes of an image (the “what”) such as color, shape, and pattern. The dorsal pathway is important for visuospatial analysis (the “where”) and for guiding movements toward items of interest. In addition, interconnecting pathways are crucial for transferring information from the primary cortex to the associative areas (V2–V5).

In general, *cortical syndromes* due to abnormal visual processing result from either damage to the cortical areas responsible for processing information or from interruption of information flow between cortical areas (*disconnection syndromes*). Disorders of higher cortical visual function may be further subdivided into disorders of object recognition, visual-spatial relationships, and awareness of visual deficit (Table 6-2).

Girkin CA, Miller NR. Central disorders of vision in humans. *Surv Ophthalmol*. 2001;45(5):379–405.

Table 6-2 Disorders of Higher Cortical Function

Disorders of recognition
Akinetopsia
Alexia without agraphia
Cerebral achromatopsia
Object agnosia
Prosopagnosia
Disorders of visual-spatial relationships
Acquired ocular motor apraxia
Optic ataxia
Simultanagnosia
Visual allesthesia
Disorders of awareness of vision or vision loss
Anton syndrome
Blindsight
Hemispatial neglect
Riddoch phenomenon

Disorders of Recognition

Object agnosia

Interruption of signal flow from the occipital lobe to the area of the temporal lobe involved in object identification results in an inability to recognize objects termed *object agnosia*. The condition, which is a form of visual–visual disconnection, often results from a bilateral ventral pathway dysfunction that affects occipitotemporal projections. Patients with object agnosia can identify objects by touch or description but not by sight.

Prosopagnosia

Prosopagnosia, the inability to recognize familiar faces, is a more specific form of visual–visual disconnection. It is more frequently congenital, with acquired cases resulting predominantly from stroke. Patients usually have difficulty performing other visual memory tasks. The condition usually occurs with bilateral inferior occipitotemporal lobe damage but may also occur with right inferior occipital lobe damage. Accompanying superior homonymous visual field defects are common.

Schmidt D. Neuro-ophthalmological findings in patients with acquired prosopagnosia. *Graefes Arch Clin Exp Ophthalmol*. 2015;253(3):333–334.

Akinetopsia

Patients with pathology affecting the dorsal pathway (area V5; also known as MT, medial temporal area) may experience akinetopsia, which is the loss of the perception of visual motion, but still retain perception of form, texture, and color.

Alexia without agraphia

The interruption of visual information between the occipital lobe and the dominant angular gyrus causes visual–verbal disconnection. During the act of reading, the right occipital lobe receives visual information from the left visual field. This information is transferred to the left side of the brain through the corpus callosum and then relayed anteriorly to the angular gyrus of the parietal lobe for comprehension. If the splenium of the corpus callosum is damaged, the information from the left visual field (right occipital lobe) cannot cross to the opposite hemisphere (Fig 6-1). Typically, the left occipital lobe is also damaged and no visual input reaches the angular gyrus, resulting in alexia (ie, the patient cannot read); however, because the structures anterior to the splenium are intact, the patient can produce language and write (alexia without agraphia). These patients cannot read what they have just written! This condition is usually due to infarction. If the left angular gyrus is damaged, then both reading and writing will be affected (*alexia with agraphia*). Such patients also often have acalculia, right–left confusion, and finger agnosia (*Gerstmann syndrome*).

Cerebral achromatopsia

Color discrimination may be abnormal with bilateral inferior occipitotemporal lobe lesions (lingual and fusiform gyrus; see Chapter 1). Affected patients cannot match colors or order them according to hue. Bilateral occipital ventromedial cortex damage may cause complete achromatopsia. Unilateral damage may cause only hemiachromatopsia. Accompanying superior homonymous visual field defects are often present.

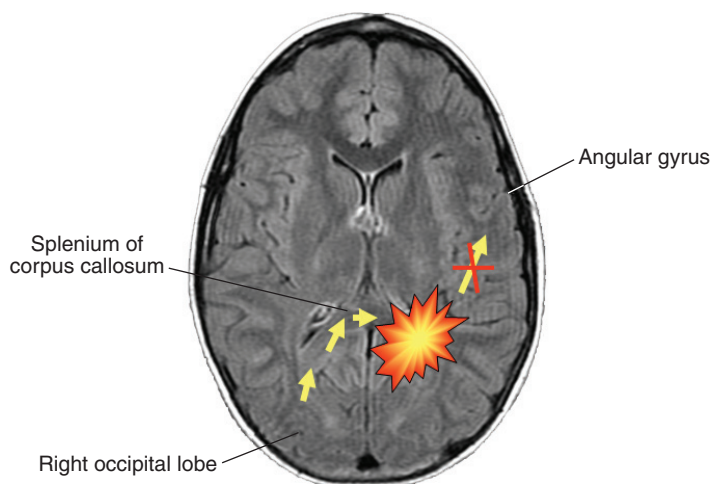


Figure 6-1 Alexia without agraphia. The diagram depicts the flow of information (*arrows*) from the right occipital lobe through the splenium of the corpus callosum to the angular gyrus. A lesion (*bright-colored polygon*) in the left occipital lobe obstructs this flow. (Courtesy of Eric Eggenberger, DO.)

Disorders of Visual-Spatial Relationships

Simultanagnosia

Simultanagnosia, which is the failure to integrate multiple elements of a scene to form the total picture, can be assessed by asking patients to describe a picture scene (Fig 6-2). A patient with simultanagnosia will describe only part of the picture and not the other portions unless the examiner identifies them. Testing color vision with the Ishihara pseudoisochromatic color plates may suggest simultanagnosia if the patient can identify colors but not the shapes of numbers (ie, the patient does not see the whole picture as the sum of its parts).

Balint syndrome

Balint syndrome is a rare phenomenon resulting from bilateral occipitoparietal lesions and consists of the triad of simultanagnosia, optic ataxia (disconnection between visual input and the motor system), and acquired ocular motor apraxia (loss of voluntary movement of the eyes while fixating on a target). Clinically, this triad of findings rarely occurs together.

Visual allesthesia

Patients with visual allesthesia see their environment as rotated, flipped, or inverted. These symptoms localize the lesion to either the lateral medullary region (*Wallenberg syndrome*) or the occipitoparietal area.

Disorders of Awareness of Vision or Visual Deficit

Anton syndrome

Patients with Anton syndrome characteristically have cortical blindness but deny having any visual problem. These patients have no demonstrable visual behavior, but they

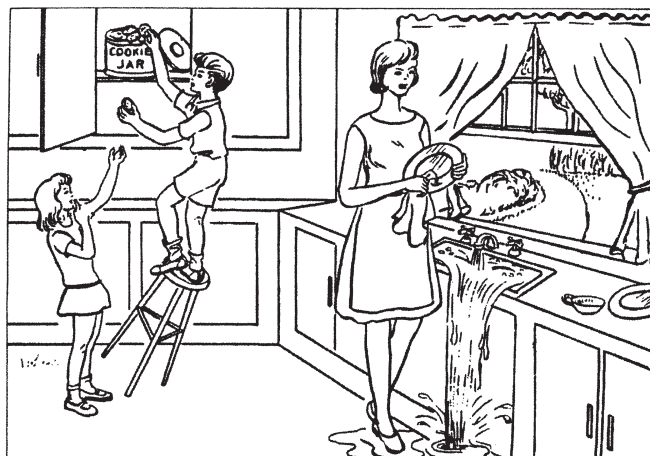


Figure 6-2 The patient is asked to describe what is occurring in this drawing, the “cookie theft picture,” modified from the Boston Diagnostic Aphasia Examination. A patient with simultanagnosia will describe one part of the scene and not see anything else. (Used with permission from Kline LB, Bajandas FJ. *Neuro-Ophthalmology Review Manual*. Rev. 5th ed. Thorofare, NJ: Slack; 2004:227.)

hallucinate and confabulate visual images, claiming the ability to see. Anton syndrome is most common with bilateral occipital infarctions but has been described with blindness from bilateral optic nerve lesions.

Riddoch phenomenon

Preservation of the perception of motion in a blind hemifield is termed staticokinetic dissociation, or the Riddoch phenomenon. When present in an otherwise complete homonymous hemianopia, it is thought to portend a better visual prognosis.

Blindsight

Cortically blind patients may have an unconscious rudimentary visual perception (blindsight). This condition manifests in the presence of damage to retrogeniculocalcarine visual pathways.

Hemispatial neglect

Patients with hemispatial neglect (hemineglect) will not acknowledge seeing objects in one hemifield (usually the left) if presented with simultaneous stimuli in both hemifields; however, they will see the stimulus if it is presented in that hemifield alone. Confrontation visual field testing using double simultaneous stimulation may be used to verify this condition (see Chapter 3). Hemispatial neglect usually results from damage in the right hemisphere (eg, the posterior parietal cortex, frontal eye fields, cingulate gyrus) that mediates attention in both hemifields.

The Patient With Abnormal Ocular Motility or Diplopia



This chapter includes related videos, which can be accessed by scanning the QR codes provided in the text or going to www.aao.org/bcscvideo_section05.

Most patients with acquired ocular motility disorders will have diplopia unless the motility limitation is symmetric. Depending on their motility limitation, some patients without diplopia in primary gaze may develop diplopia in horizontal or vertical gaze. Diplopia can also occur in patients with full ocular motility. Answers to the following questions, which are discussed in this chapter, offer important insight into the nature of a patient's diplopia:

- Does the diplopia resolve when either eye is covered (monocular vs binocular diplopia)?
- Is the diplopia horizontal, vertical, oblique, or torsional?
- Is the diplopia the same in all fields of gaze (*comitant*) or does it vary with gaze direction (*incomitant*)?
- Is the diplopia constant, intermittent, or variable?

History

Patients with an ocular misalignment may report double vision or simply “blurred vision.” If closing either eye eliminates the visual disturbance, the blurred vision can be attributed to ocular misalignment (“binocular blur”). If binocular diplopia resolves when the patient closes either eye, it is because the diplopia results from misalignment of the visual axes. It is helpful to determine if the double vision is more bothersome with far or near fixation, or in a particular position of gaze. Ascertaining whether the patient has a history of head or eye pain, eye or eyelid swelling or redness, numbness, or other neurologic symptoms provides clues about possible orbital, cavernous sinus, or central nervous system causes of diplopia. It is also important to establish whether there is any history of malignancy, trauma, thyroid disease, or generalized weakness when formulating a differential diagnosis for binocular diplopia.

Physical Examination

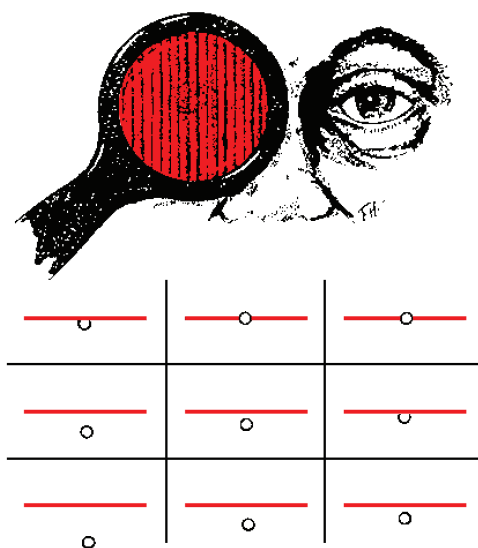
Maintaining alignment of the visual axes depends on coordinating the movement of both eyes. External examination may reveal obvious clues for the etiology of the patient's diplopia, especially if proptosis or ocular redness is present. The movement of the eyes should be assessed in all positions of gaze, both individually (*ductions*) and together (*versions*).

It is important to establish whether ocular misalignment is comitant or incomitant. Comitant misalignment is often present in congenital strabismus, whereas incomitant misalignment is evidence of an acquired disorder, except in rare cases. Abnormal ductions can often be recognized by gross observation, but formal measurement of the amount of misalignment with a prism and alternate cover test (PACT) is used to determine (quantitate) whether an ocular misalignment is comitant or incomitant.

The Maddox rod test, a sensitive method of obtaining quantitative information about the degree and pattern of ocular misalignment (Fig 7-1), can help reveal subtle cases of strabismus. When viewing a light source through a *red Maddox rod*, which contains a series of parallel cylinders, the patient sees a line perpendicular to the orientation of the cylinders. Typically, a red Maddox rod is placed in front of the right eye, producing a red line, while the left eye views the fixation light. Viewing such disparate images often makes it easier for patients to appreciate the misalignment of the visual axes. Because this test dissociates the 2 eyes, patients who have a phoria will also report diplopia. Therefore, it is often useful to combine the subjective results of Maddox rod tests with the more objective results of the simultaneous PACT. PACT is used to determine the manifest deviation, paying attention to the pattern of misalignment in all 9 positions of gaze (and, in some cases, to head tilt).

The double Maddox rod test helps identify and quantify torsional misalignment when vertical diplopia is present. Traditionally, a red Maddox rod is placed in front of the right eye and a white Maddox rod in front of the left eye (Fig 7-2). Because patients may assume

Figure 7-1 Maddox rod shown with the ridges held vertically, which causes the patient to see a horizontal red line. In this example, the light seen by the left eye is under the red line, indicating a left hyperdeviation, which increases on down right gaze. This finding is compatible with left superior oblique dysfunction.



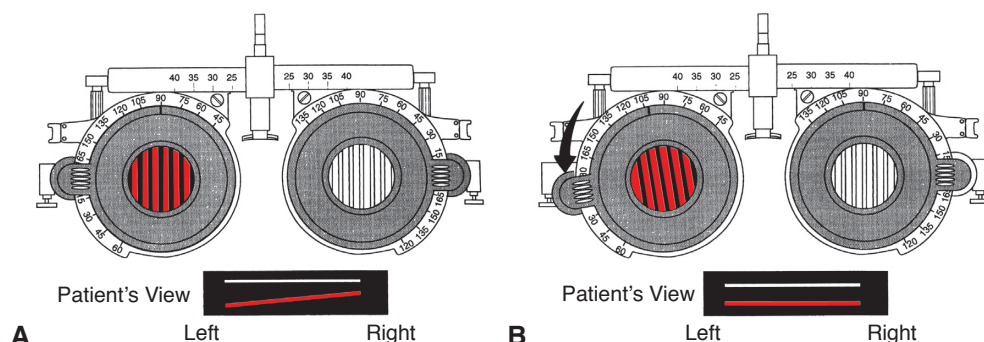


Figure 7-2 Double Maddox rod test for extorsion. **A**, A patient with vertical diplopia sees the red line below the white line, indicating a right hypertropia. **B**, With cyclotorsion, the 2 lines do not appear parallel. The red Maddox rod is then rotated (*large arrow*) until the 2 lines appear parallel. The degree of rotation required to make the lines appear parallel (in this case about 12°) quantitates the amount of extorsion. (Used with permission from Kline LB, Bajandas FJ. *Neuro-Ophthalmology Review Manual*. Rev. 5th ed. Thorofare, NJ: Slack; 2004. Originally modified from Van Noorden GK. *Atlas of Strabismus*. 4th ed. St Louis: Mosby; 1983.)

that the white line is oriented correctly and falsely localize the abnormal torsion to the red line (right eye), this test is best performed with a red lens in front of each eye.

A qualitative method for detecting relative cyclotropia uses a horizontal line. A base-down prism is placed over 1 eye to dissociate the images such that 2 vertically displaced lines are visible. The patient is asked whether both lines are parallel or if they converge to 1 side. A cranial nerve (CN) IV palsy is typically associated with convergence of the lines toward the side of the palsy. A CN IV palsy may also be suspected if indirect ophthalmoscopy reveals appreciable extorsion of the ipsilateral fundus (ie, the fovea appears above the superior margin of the optic nerve head).

The presence of ocular deviation may be signaled by a consistent head tilt or head turn on examination. Old photographs (eg, a driver's license photograph) may provide evidence of chronicity.

Simons K, Arnoldi K, Brown MH. Color dissociation artifacts in double Maddox rod cyclodeviation testing. *Ophthalmology*. 1994;101(12):1897–1901.

Monocular Diplopia

As mentioned, patients may describe optical aberrations as distorted or double vision. Monocular diplopia usually results from abnormalities of the refractive media (eg, uncorrected astigmatism, corneal irregularities such as keratoconus and tear film abnormalities, and cataract). The characteristics of optical causes are seeing ghost images, haloes, or more than 2 images. Monocular diplopia that resolves with use of a pinhole proves there is an optical etiology, obviating the need for a neurologic workup. Less commonly, monocular diplopia can arise from retinal pathology (eg, maculopathy with retinal distortion by fluid, hemorrhage, or fibrosis). Cerebral monocular diplopia or polyopia is always bilateral and extremely rare.

Differentiating Paretic From Restrictive Etiologies of Diplopia

Restriction of eye movements should be strongly suspected in patients with proptosis, enophthalmos, or a history of orbital trauma or eye surgery. The most common causes of restrictive strabismus are thyroid eye disease and orbital trauma; these conditions are typically associated with orbital signs and symptoms. Diplopia in these patients may have both neural and restrictive components, especially after trauma.

Paretic and restrictive syndromes may be distinguished by assessing saccadic speed. Paretic conditions reduce saccadic velocity, whereas restrictive conditions do not. If this method does not provide an answer, then the examiner may perform a *forced duction test* (Fig 7-3). A restrictive process produces a mechanical limitation of the range of eye movements that can often be felt by the examiner when forceps or a cotton swab is used to advance the limited eye movement. In rare cases, chronic neural lesions may also cause mechanical limitation by gradual shortening of the unopposed antagonist muscle; therefore, a “tight” muscle may give a false-positive result.

Comitant and Incomitant Deviations

As previously mentioned, comitant misalignment is characteristically found in patients with congenital or early-onset strabismus. Patients with this condition typically do not report diplopia because of *suppression*, an adaptation that reduces the responsiveness of the visual neurons in the occipital cortex to the input from 1 eye (see BCSC Section 6, *Pediatric Ophthalmology and Strabismus*, Chapter 5, Fig 5-5). Patients with a history of childhood strabismus may experience diplopia later in life if their ocular misalignment changes. For example, in patients with a long-standing exophoria, horizontal diplopia may develop in the fifth decade of life, when accommodation and convergence capacities wane.

Conversely, an incomitant deviation may become comitant with the passage of time. This spread of comitance may occur with either a restrictive or paretic incomitant deviation and is especially likely with a CN IV palsy.

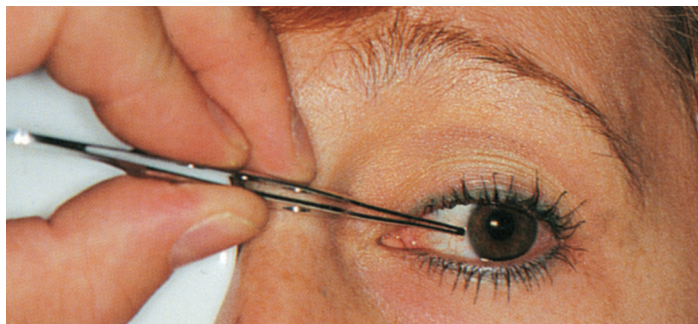


Figure 7-3 Forced duction testing. Before the eye is grasped with forceps, topical proparacaine drops are applied to the eye and held over the limbal region with a cotton tip for 1–2 minutes. This patient has a left esotropia and limited abduction. The conjunctiva is grasped with toothed forceps and the globe passively rotated in the direction of limited abduction to assess for restriction of the eye movement. (Used with permission from Yanoff M, Duker JS, eds. *Ophthalmology*. 2nd ed. St Louis: Mosby; 2004:569, Fig 70-12.)

Incomitant strabismus is most frequently acquired and usually causes diplopia. If the deviation is very small, fusion may align the eyes and eliminate diplopia. Relatively small misalignments may produce blurred vision rather than an obvious perception of 2 images. Patients with subnormal vision may not recognize diplopia or may have difficulty articulating how their visual perception changes in various positions of gaze. Congenital incomitant deviations, such as those caused by overaction of the inferior oblique muscles, typically do not produce diplopia, even when the strabismus is quite obvious. Generally, gross observation alone is not sufficient for the clinician to distinguish with confidence whether subnormal ductions are secondary to a paretic or restrictive process.

Localization

Because many eye movement disorders have a neural basis, the clinician should attempt to localize the potential lesion that might be producing the patient's eye movement disorder. Anatomical localization will dictate patient evaluation, including imaging modality and differential diagnosis. It is also useful to conceptualize the anatomical pathway of the ocular motor system (ie, extraocular muscles, neuromuscular junction, orbit, CNs, brainstem, premotor input, and cerebrum) that is assumed to be involved (Fig 7-4). Adopting this kind of "wiring diagram" approach takes into account the supranuclear, internuclear,

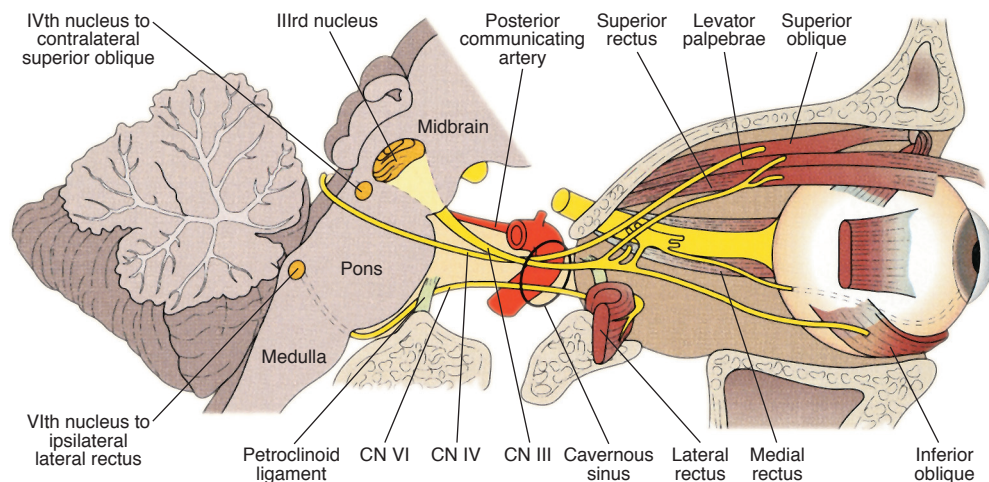


Figure 7-4 Anatomical substrate for localizing lesions of the infranuclear ocular motor pathways. This schematic provides a lateral view of CNs III, IV, and VI from the brainstem nuclei to the orbit. A sequential consideration of these pathways could begin either within the brainstem or within the orbit. The cranial nerve segments within the brainstem are often referred to as being "intramedullary." The subarachnoid space lies between the brainstem and cavernous sinus. CN III exits the midbrain anteriorly, crosses near the junction of the internal carotid and posterior communicating arteries in the subarachnoid space, and enters the cavernous sinus, where it runs in the lateral wall. CN IV exits the midbrain posteriorly and crosses to the opposite side. It then courses through the subarachnoid space and into the cavernous sinus. CN VI exits the pons anteriorly, ascends along the clivus, crosses the petrous apex, and passes below the petroclinoid ligament to enter the cavernous sinus, where it runs between the lateral wall and the carotid artery. (Used with permission from Yanoff M, Duker JS, eds. *Ophthalmology*. 2nd ed. St Louis: Mosby; 2004:1324, fig 199-1.)

nuclear, and fascicular pathways within the brainstem, which then traverse the subarachnoid space, cavernous sinus, superior orbital fissure, and orbit, ending in the neuromuscular junctions of the extraocular muscles. In general, a lesion involving the CN nucleus or fascicle will cause neurologic deficits in addition to ophthalmoparesis (discussed later in the chapter). Central lesions can produce a clinically isolated CN III, IV, or VI palsy, but such isolated cranial neuropathies are the exception.

Attempts at neural localization may fail or give false results in the presence of diffuse disease (eg, meningeal inflammation, as in sarcoidosis). In addition, this approach is not helpful in a clinical syndrome, such as Wernicke encephalopathy, in which imaging may not show characteristic structural disturbances.

Supranuclear Causes of Abnormal Ocular Motility

Most supranuclear disorders affect both eyes equally and therefore do not cause diplopia. However, certain supranuclear lesions do not result in a symmetric effect and thus may produce ocular misalignment and diplopia (Table 7-1; also see Chapter 8).

Nuclear Causes of Diplopia

The CN III nucleus is actually a nuclear complex that contains subnuclei for 4 extraocular muscles (superior, inferior, medial recti, and inferior oblique), a single subnucleus (central caudal nucleus) for the levator palpebrae muscles, and paired subnuclei (Edinger-Westphal nuclei) for the pupillary constrictor muscles (see Chapter 1). Because the single central caudal nucleus controls both levator palpebrae superioris muscles, and the superior rectus fascicles decussate just after emerging from their subnuclei, lesions of the CN III nuclear complex either affect or spare both upper eyelids and may affect the contralateral superior rectus muscle. Injury to the CN III nuclear complex, while uncommon, may occur secondary to reduced perfusion through a small, paramedian-penetrating blood vessel, causing unilateral damage to 1 nuclear complex. Such lesions are often asymmetric and may affect the CN III fascicle on one side in addition to the nucleus.

Intraparenchymal (either nuclear or intra-axial) lesions of CN IV are rare, given the relatively short course of the nerve within the brainstem. A lesion of the CN IV nucleus is clinically identical to a fascicular lesion. Microvascular, inflammatory, neoplastic, or demyelinating lesions may involve the central course of CN IV. Occasionally, a CN IV palsy may be accompanied by a contralateral Horner syndrome (first-order neuron lesion)

Table 7-1 Supranuclear Ocular Motor Lesions That Produce Strabismus and Diplopia

Convergence insufficiency or spasm
Divergence insufficiency
Ocular tilt reaction
Skew/alternating skew deviation
Thalamic esodeviation

because of the proximity of the descending sympathetic pathway to the caudal portion of the nucleus. A relative afferent pupillary defect may also be associated with a CN IV palsy due to the pupillary fibers running in the nearby brachium of the superior colliculus.

A selective lesion of the CN VI nucleus causes a horizontal gaze palsy and not an isolated abduction paresis in 1 eye; therefore, patients with this lesion may not experience diplopia. This occurs because the CN VI nucleus contains 2 populations of motoneurons: (1) those that innervate the ipsilateral lateral rectus muscle and (2) those that travel via the medial longitudinal fasciculus to innervate the contralateral medial rectus subnucleus of the CN III nuclear complex. Often, ipsilateral upper and lower facial weakness is also present with a nuclear CN VI palsy due to the adjacent facial nerve fascicle (eg, facial colliculus syndrome).

Elliott D, Cunningham ET Jr, Miller NR. Fourth nerve paresis and ipsilateral relative afferent pupillary defect without visual sensory disturbance. A sign of contralateral dorsal midbrain disease. *J Clin Neuroophthalmol*. 1991;11(3):169–172; discussion 173–174.

Internuclear Causes of Diplopia

In the context of eye movement control, an “internuclear” lesion is one that disrupts the *medial longitudinal fasciculus* (MLF), a bundle of fibers that connects the CN VI nucleus on one side of the pons to the medial rectus subnucleus (of CN III) on the contralateral side of the midbrain (see Chapter 1, Fig 1-27). This type of lesion produces an *internuclear ophthalmoplegia* (INO).

Internuclear Ophthalmoplegia

The cardinal sign of a unilateral INO is slowed adducting saccadic velocity in 1 eye, usually associated with abducting nystagmus of the fellow eye. The eye with the slowed adduction may have a full or limited range of adduction (Video 7-1; Fig 7-5). Convergence may be spared or disrupted. A skew deviation, often with hyperdeviation ipsilateral to the lesion, may be present. The INO is named for the side with slowed adduction (ie, a right INO refers to slowed adduction of the right eye secondary to a MLF lesion on the right side of the brainstem). Patients with INO may report horizontal diplopia; they may also experience vertical-oblique diplopia due to an associated skew deviation, episodic diplopia related to head–eye movements if the lesion is partial, or difficulty tracking fast-moving objects (eg, when playing sports) because of the mismatch in saccadic velocity between the eyes.



VIDEO 7-1 Left internuclear ophthalmoplegia.

Courtesy of M. Tariq Bhatti, MD.

Access all Section 5 videos at www.aao.org/bcscvideo_section05.



A bilateral INO produces bilateral adduction lag, bilateral abducting nystagmus, and *vertical, gaze-evoked nystagmus* that is most noticeable in upgaze. This nystagmus is due to disruption of vertical vestibular pursuit and gaze-holding pathways, which ascend from the vestibular nuclei through the MLF. A large-angle exotropia may occur in bilateral INO (ie, “wall-eyed” bilateral INO, or *WEBINO*, syndrome) and is often caused by a midbrain lesion near the CN III nuclei.

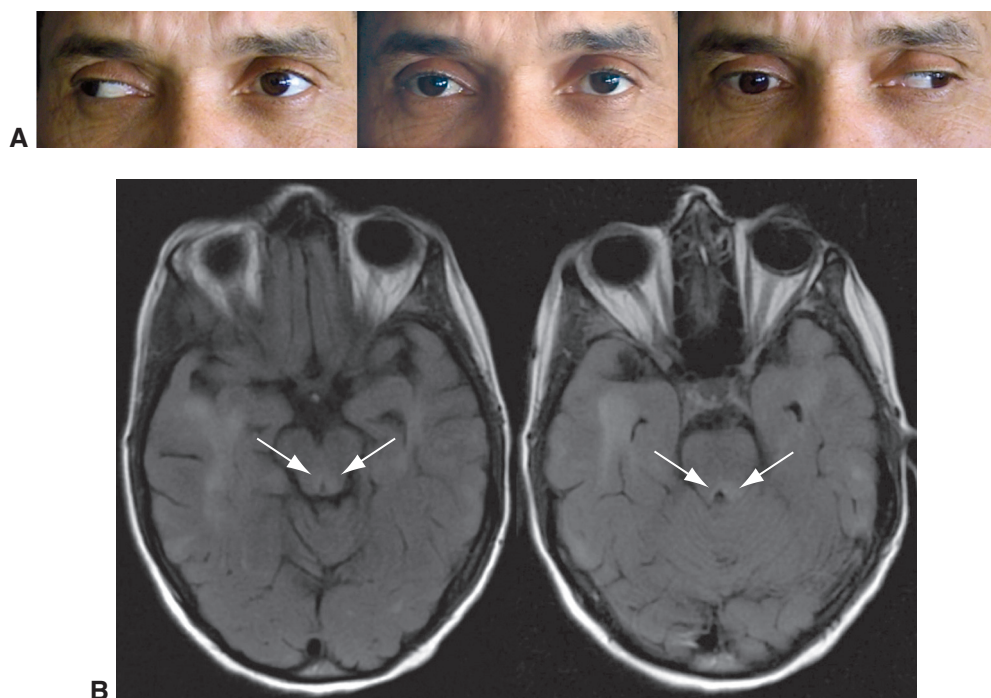


Figure 7-5 Bilateral internuclear ophthalmoplegia (INO) in a 53-year-old man with diplopia on lateral gazes. **A**, Horizontal gaze in either direction results in full abduction of the ipsilateral eye but virtually no adduction of the contralateral eye. Alignment in primary gaze (*center panel*) is nearly orthotropic. **B**, Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) brain scan showing edema (bright signal indicated by *arrows*) in the area of the medial longitudinal fasciculus bilaterally at the level of the upper midbrain (*left*) and pons (*right*). (Courtesy of Prem S. Subramanian, MD, PhD.)

The 2 most common causes of INO are demyelination and stroke. In adolescents and younger adults, INO is typically caused by demyelination. In older adults, microvascular disease is the most common cause. Other causes include infection, neoplasm, trauma, and progressive supranuclear palsy (PSP). Myasthenia gravis can produce pseudo-INO, which usually lacks the vertical gaze-evoked nystagmus of a true INO and is often accompanied by myasthenic eyelid signs. The adduction paresis of myasthenic pseudo-INO may resolve transiently after intravenous administration of edrophonium and typically responds to appropriate systemic therapy (see Chapter 14).

Amezcu L, Morrow MJ, Jirawuthiworavong GV. Multiple sclerosis: review of eye movement disorders and update of disease-modifying therapies. *Curr Opin Ophthalmol*. 2015;26(6):534–539.

Frohman TC, Galetta S, Fox R, et al. Pearls & Oy-sters: the medial longitudinal fasciculus in ocular motor physiology. *Neurology*. 2008;70(17):e57–e67.

McGettrick P, Eustace P. The W.E.B.I.N.O. syndrome. *Neuro-Ophthalmology*. 1985;5:109–115.

Mills DA, Frohman TC, Davis SL, et al. Break in binocular fusion during head turning in MS patients with INO. *Neurology*. 2008;71(6):458–460.



Figure 7-6 One-and-a-half syndrome. This 15-year-old patient had a brainstem glioma that caused a gaze palsy to the left (*right photograph*) and a left INO (evident here as incomplete adduction of the left eye on gaze to the right; *left photograph*). The only horizontal eye movement was abduction of the right eye. (Courtesy of Steven A. Newman, MD.)

One-and-a-Half Syndrome

One-and-a-half syndrome, which combines a horizontal gaze palsy and ipsilateral INO (Fig 7-6), is caused by a pontine abnormality that is large enough to involve the MLF and the paramedian pontine reticular formation (PPRF) or the CN VI nucleus on the same side of the brainstem. The only horizontal eye movement remaining is abduction of the eye contralateral to the lesion (ie, horizontal eye movements are lost in 1 eye, whereas they are “half” lost in the fellow eye, hence the name). Vertical gaze is preserved. A lesion that produces one-and-a-half syndrome but also involves the intra-axial portion of CN VII is termed *eight-and-a-half syndrome* ($7 + 1.5 = 8.5$). Stroke is the most common cause of this disorder.

Espinosa PS. Teaching NeuroImage: one-and-a-half syndrome. *Neurology*. 2008;70(5):e20.
 Johkura K, Kudo Y, Amano Y, et al. Gaze palsy and exotropia in internuclear ophthalmoplegia. *J Neurol Sci*. 2015;353(1–2):158–160.

Infranuclear Causes of Diplopia

Intra-axial (*fascicular*) ocular motor CN palsies are due to lesions of the nerve distal to its nucleus but within the confines of the brainstem. Brainstem lesions tend to affect many structures and therefore produce numerous deficits, allowing accurate topographic localization of the lesion. In the midbrain, intra-axial lesions can damage either CN III or CN IV. Intra-axial involvement of the CN III fascicle can produce 1 of 4 syndromes, each of which includes an ipsilateral CN III palsy:

1. Damage to the ventral midbrain and the cerebral peduncle can cause a contralateral hemiparesis (*Weber syndrome*).
2. Involvement of the red nucleus and substantia nigra may produce contralateral ataxia or tremor (*Benedikt syndrome*).
3. Damage to the dorsal midbrain may involve the superior cerebellar peduncle and produce contralateral ataxia (*Claude syndrome*).
4. Dorsal lesion with a slightly different configuration can produce the same type of ataxia plus a CN III nuclear lesion and features of supranuclear eye movement dysfunction (*Nothnagel syndrome*).

The localization and direct anatomical correlations of these lesions are more important than the eponyms, especially because the use and definitions of these eponyms have varied in the literature.

As mentioned, involvement of CN IV within the brainstem is uncommon. Pineal tumors may compromise the proximal course of both CNs IV by compressing the tectum of the midbrain. Such lesions may also obstruct the Sylvian aqueduct, leading to elevated intracranial pressure and hydrocephalus, as well as dorsal midbrain syndrome (see Chapter 8).

Intra-axial lesions of the CN VI nucleus may also injure CN VII, whose fibers curve around the CN VI nucleus at the *facial genu* (see Chapter 1, Fig 1-36). Intra-axial lesions that involve the CN VI fascicle may also damage the CN VII fascicles, the tractus solitarius, and the descending tract of CN V, resulting in an ipsilateral abduction palsy, facial weakness, loss of taste over the anterior two-thirds of the tongue, and facial hypoesthesia (*Foville syndrome*). Lesions of the ventral pons can damage CN VI and CN VII along with the corticospinal tract, producing contralateral hemiplegia, ipsilateral facial weakness, and abduction deficit (*Millard-Gubler syndrome*).

The subarachnoid segment of the ocular motor CNs extends from the brainstem to the cavernous sinus, where the nerves exit the dura. It is believed that most ischemic CN palsies occur within this section. Ischemic cranial mononeuropathies typically occur in isolation, with maximal deficit at presentation, but occasionally the loss of function progresses over 7–10 days. Pain may or may not be present; if present, it may be quite severe in some patients. Therefore, pain does not distinguish ischemia from aneurysmal compression.

Ocular misalignment due to ischemic ocular motor CN palsy almost always improves over time, and the diplopia usually resolves within 6 months. Patients require medical evaluation for ischemic risk factors, including diabetes mellitus, hypertensive vascular disease, and elevated serum lipid levels. Progression of ocular misalignment beyond 2 weeks or failure to improve within 3 months is inconsistent with an ischemic cause of a cranial neuropathy and should prompt a thorough evaluation for another etiology. An isolated mononeuropathy of CN III warrants special attention because of the nerve's close anatomical proximity to the cerebral vasculature (especially the posterior communicating artery) and the potential for aneurysmal compression (discussed later in this chapter).

Myasthenia gravis may mimic any pattern of painless, pupil-sparing extraocular muscle dysfunction and should be included in the differential diagnosis of such cases. Approximately 10%–15% of patients with giant cell arteritis (GCA) may present with diplopia from a skew deviation, ischemic cranial neuropathy, or extraocular muscle ischemia.

If the patient has a history of cancer and an ocular motor cranial neuropathy is present, neuroimaging should be performed to rule out a compressive or infiltrative lesion.

Asbury AK, Aldredge H, Hershberg R, Fisher CM. Oculomotor palsy in diabetes mellitus: a clinico-pathological study. *Brain*. 1970;93(3):555–566.

Comer RM, Dawson E, Plant G, Acheson JF, Lee JP. Causes and outcomes for patients presenting with diplopia to an eye casualty department. *Eye (Lond)*. 2007;21(3):413–418.

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Third Cranial Nerve Palsy

CN III palsies can cause dysfunction of the somatic muscles (superior, inferior, and medial recti; inferior oblique; and levator palpebrae superioris) and the autonomic muscles (pupillary sphincter and ciliary) (Video 7-2). A complete CN III palsy presents with downward and outward deviation of the eye; complete ptosis; and the inability to adduct, infraduct, or supraduct the eye. The pupil may or may not be involved in a complete CN III palsy. Pupillary involvement, which is discussed later in the chapter, is a critical distinction in the setting of a CN III palsy. Partial CN III palsies are more common; they present with variable limitation of supraduction, infraduction, adduction, and variable ptosis with or without pupillary dysfunction (Fig 7-7).



VIDEO 7-2 Right CN III palsy.

Courtesy of M. Tariq Bhatti, MD.

Access all Section 5 videos at www.aao.org/bcscvideo_section05.

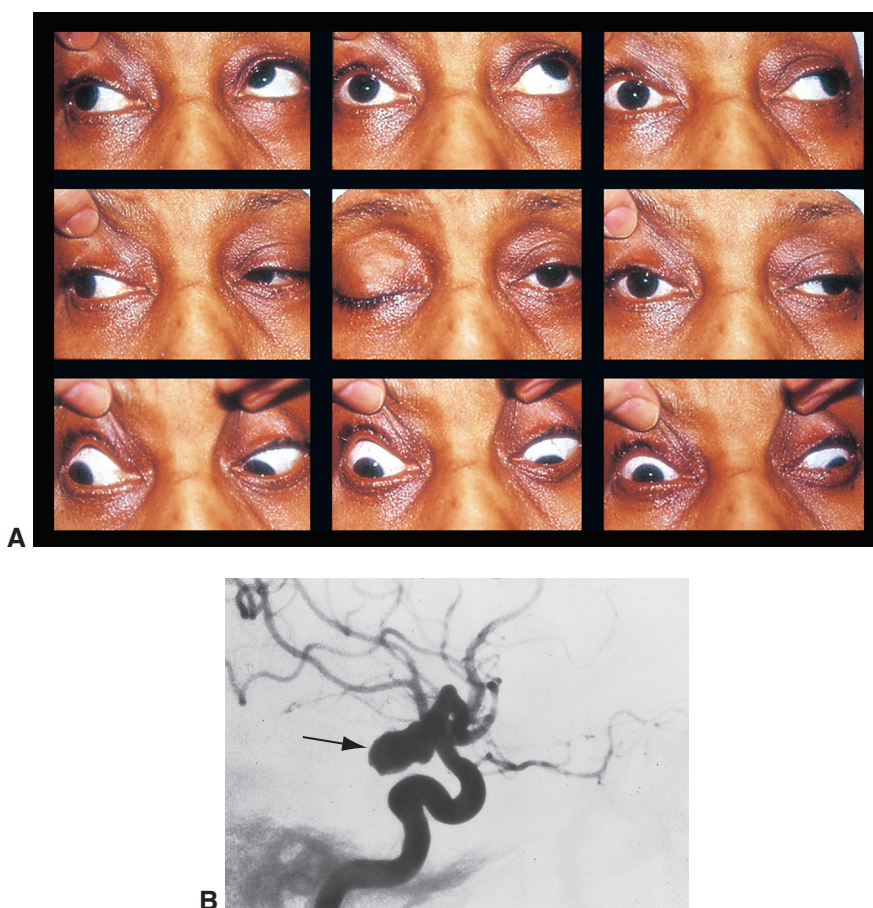


Figure 7-7 Partial CN III palsy. This 62-year-old woman reported experiencing “the worst headache of my life.” **A**, Examination revealed complete ptosis on the right; a nonreactive, dilated pupil; and severely limited extraocular movement except for abduction. **B**, Lateral view of a cerebral angiogram demonstrated a posterior communicating artery aneurysm (arrow). (Part A courtesy of Steven A. Newman, MD; part B courtesy of Leo Hochhauser, MD.)

Most isolated unilateral CN III palsies result from (presumed) microvascular injury in the subarachnoid space or cavernous sinus. Less common causes include aneurysmal compression, tumor, inflammation (eg, sarcoidosis), vasculitis, infection (eg, meningitis), infiltration (eg, lymphoma, carcinoma), and trauma.

Pupil-involving third cranial nerve palsy

Pupillary dysfunction with CN III palsy results from loss of parasympathetic input and produces a mid-dilated pupil that responds poorly to light. Patients may present with variable dysfunction of the levator palpebrae or extraocular muscles. Aneurysms that arise at the junction of the posterior communicating artery (PCoA) and internal carotid artery (ICA) are juxtaposed to CN III and are, therefore, in a position to produce a CN III palsy as the initial manifestation of aneurysmal expansion or rupture. Pupillary involvement occurs because the pupillomotor fibers reside superficially in the medial aspect of the nerve adjacent to the PCoA (see Chapter 1, Fig 1-31). Thus, until proven otherwise, the clinician must assume that a nontraumatic CN III palsy with pupillary involvement or evidence of progression to pupillary involvement is secondary to an aneurysm. Emergent cerebrovascular imaging (eg, catheter angiography, magnetic resonance angiography [MRA], or computed tomography angiography [CTA], depending on clinical scenario and neuroradiologic consultation) should be undertaken (Fig 7-8). These angiographic methods can detect almost all aneurysms at this location that produce a CN III palsy. Modern CTA and MRA techniques can reliably detect aneurysms as small as 3 mm in diameter. Of these 2 methods, CTA is faster, provides images with slightly greater resolution, and may show evidence of a subarachnoid hemorrhage. Routine magnetic resonance imaging (MRI) acquired with the MRA is more likely to show

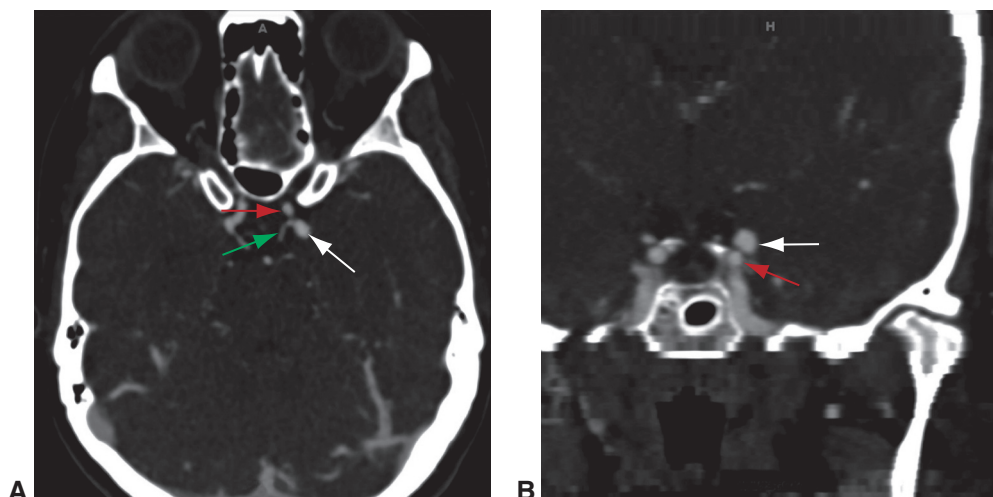


Figure 7-8 Computed tomographic angiography (CTA) demonstrates an aneurysm of the left posterior communicating artery. **A**, Axial and **B**, coronal views show the aneurysm (*white arrows*) at the junction of the internal carotid artery (*red arrows*) and posterior communicating artery (*green arrow*). The patient presented with a pupil-involving partial left CN III palsy. (Courtesy of Prem S. Subramanian, MD, PhD.)

nonaneurysmal lesions. When neuroimaging appears normal, lumbar puncture may yield evidence of a subarachnoid hemorrhage (xanthochromia of the spinal fluid) or detect an inflammatory or neoplastic cause. Catheter angiography is often used for diagnostic confirmation and definitive treatment of the aneurysm but rarely for diagnosis alone. Although aneurysms are uncommon in patients younger than 20 years, in rare cases they may present as early as the first decade of life.

A patient who presents only with efferent pupillary dysfunction (ie, the pupil is dilated and responds poorly to light) but exhibits normal eyelid and extraocular muscle function almost always has a benign disorder. Such isolated pupillary involvement is not a form of CN III palsy but rather represents a pupil that is either tonic (Adie), pharmacologically dilated, or mechanically damaged (see Chapter 10). Before concluding that the problem is limited to the pupil, the clinician must exclude minor degrees of incomitant strabismus (via careful PACT or Maddox rod testing) in order to exclude a subtle CN III palsy. Tentorial herniation is not a plausible explanation for an isolated, fixed, and dilated pupil in the absence of altered mental status or other neurologic abnormalities.

Pupillary dysfunction, or a progressive loss of function, does not always indicate the presence of an aneurysm or other serious problem. The vasculopathic form of a CN III palsy may produce some efferent pupillary defect in up to 20% of cases, although the pupillary involvement is generally mild (typically ≤ 1 mm anisocoria). Elevated fasting blood glucose, hemoglobin A_{1c}, serum lipid levels, or blood pressure indicate an increased probability that microvascular ischemia is the cause of the CN III palsy; however, patients with these risk factors may also harbor aneurysms. Thus, pupillary involvement should prompt neuroimaging in search of an aneurysm.

Pupil-sparing third cranial nerve palsy

The term *pupil-sparing complete CN III palsy* should be reserved for cases in which pupillary function is normal (ie, equal pupil size and reactivity), but there is total loss of eyelid and ocular motor functions of CN III. These are the typical findings for ischemic cranial neuropathy, which usually fully resolves within 6 months. A pupil-sparing complete CN III palsy is almost always benign and secondary to microvascular disease (diabetes mellitus, hypertension, or hyperlipidemia). An acute, isolated, pupil-sparing (but otherwise complete) CN III palsy in a patient over 50 years of age with known vascular risk factors and without history of cancer does not necessarily require neuroimaging. However, a general medical evaluation is indicated to assess the patient's serum glucose levels, systemic blood pressure, and serum lipid levels. In older adults, screening for vasculitis (eg, GCA) using Westergren sedimentation rate, C-reactive protein, and platelets must also be considered. If progression occurs, other cranial neuropathies develop, or the expected improvement does not ensue within 3 months, then neuroimaging should be undertaken to search for a mass or infiltrative lesion at the base of the skull or within the cavernous sinus. Occasionally, neuroimaging studies need to be repeated to discover a mass, especially if it is within the cavernous sinus. Lumbar puncture may be needed to detect carcinomatous meningitis, inflammation, or infection.

In contrast, if the pupil-sparing CN III palsy is *partial*, the pupil reacts normally, with incomplete impairment of levator palpebrae and extraocular muscle function. Although

the pupil is normal, this does not have the same benign implication as in pupil-sparing but otherwise complete oculomotor paresis, given that many other fibers within CN III are also “spared.” This distinction is crucial because some partial CN III palsies with normal pupillary function are due to compressive lesions, including aneurysm, and may later progress to involve the pupil (Fig 7-9). An MRA or CTA is therefore indicated to exclude an aneurysm. If the MRA/CTA is negative and the CN III palsy has progressed on follow-up, MRI of the brain and orbits using a gadolinium contrast agent should be obtained to search for an anatomical lesion. As mentioned, if the pupil is involved in any CN III palsy, neuroimaging is indicated.

The presence of head and periorbital pain is not helpful in establishing the cause of the CN III palsy. Although most CN III palsies caused by aneurysms present with pain, many vasculopathic palsies also produce pain that, in some cases, may be intense.

Patients with partial CN III palsy secondary to aneurysm tend to have better recovery of function than patients with complete CN III palsy after undergoing the same neurosurgical intervention. Better recovery is also seen in patients with partial CN III palsy versus those with complete CN III palsy resulting from pituitary adenoma or apoplexy.

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Trobe JD. Searching for brain aneurysm in third cranial nerve palsy. *J Neuroophthalmol*. 2009;29(3):171–173.

Figure 7-9 Coronal view of CTA demonstrating a large right cavernous internal carotid artery aneurysm (*asterisk*). The patient initially presented with a pupil-sparing partial right CN III palsy that progressed with subsequent pupillary involvement. (Courtesy of Zoë R. Williams, MD.)



Divisional third cranial nerve palsy

CN III branches into superior and inferior divisions within the cavernous sinus and superior orbital fissure. Isolated involvement of either division usually indicates a lesion of the anterior cavernous sinus or posterior orbit. The initial diagnostic study of choice is cranial and orbital MRI with contrast and fat suppression in addition to an MRA. If neuroimaging results are normal, then medical evaluation is warranted, including assessment of blood pressure, blood glucose, and serum lipid levels, in addition to Westergren sedimentation rate and C-reactive protein in the appropriate clinical scenario. In rare cases, a divisional CN III palsy may be secondary to brainstem disease, usually from small-vessel stroke (lacunae) or demyelination. Aneurysms are a much less common but potentially lethal cause of divisional CN III palsy. Rare additional causes include tumors, inflammation (eg, sarcoidosis, vasculitis), infection (eg, meningitis), infiltration (eg, carcinomatous meningitis or lymphoma), and trauma.

Bhatti MT, Eisenschenk S, Roper SN, Guy JR. Superior divisional third cranial nerve paresis: clinical and anatomical observations of 2 unique cases. *Arch Neurol*. 2006;63(5):771–776.

Third cranial nerve palsy in younger patients

Children may experience transient ophthalmoplegia after a viral infection or vaccination. Although aneurysms are rare in children, a pupil-involving CN III palsy necessitates a workup to exclude an aneurysm or other structural etiology. The third edition of *The International Classification of Headache Disorders (ICHD)* recently introduced *recurrent painful oculomotor neuropathy* as the new classification for recurrent headaches with subsequent unilateral ophthalmoplegia, replacing the previous term *ophthalmoplegic migraine*. The recurrent ophthalmoplegia usually presents as a CN III palsy, and onset most often occurs in childhood. Curiously, the ophthalmoplegia develops days after the onset of head pain. MRI may demonstrate reversible thickening and enhancement at the root exit zone of CN III. CN III schwannoma may mimic the fluctuating nature of this condition; however, CN enhancement will persist after resolution of the CN III palsy. Therefore, follow-up MRI is indicated.

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Aberrant regeneration of the third cranial nerve

After nerve axons are damaged, the nerve fibers may regrow to innervate muscles other than those they originally innervated (Fig 7-10). This fiber misrouting produces several synkinetic phenomena (ie, co-contraction of muscles that normally are not activated together). Classic findings include eyelid retraction with adduction or pupillary miosis with elevation, adduction, or depression.

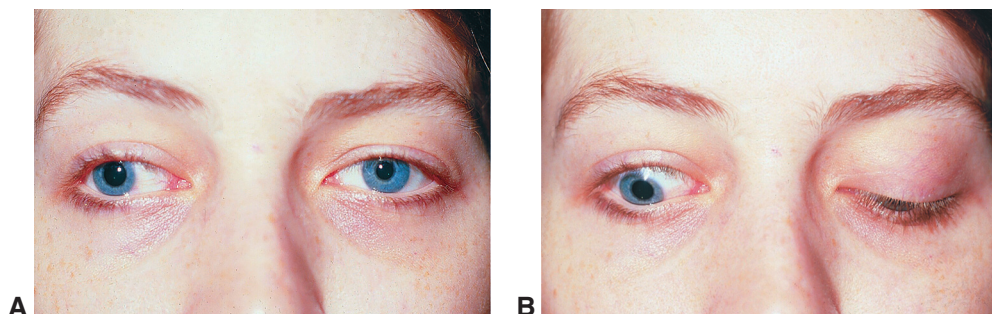


Figure 7-10 Aberrant regeneration of the right CN III. **A**, In primary gaze, there is mild ptosis, pupillary mydriasis, and exotropia, all on the right. **B**, With attempted downward gaze, the right eyelid retracts as fibers of the right CN III supplying the inferior rectus now also innervate the levator muscle. (Courtesy of Rod Foroozan, MD.)

Aberrant regeneration is common after trauma or compression by an aneurysm or tumor but does not occur with microvascular ischemia. Signs of aberrant regeneration without a history of CN III palsy—*primary aberrant regeneration*—are presumptive evidence of a slowly expanding parasellar lesion, most commonly a meningioma or carotid aneurysm within the cavernous sinus, which requires appropriate neuroimaging.

Ling JD, Chao D, Al Zubidi N, Lee AG. Big red flags in neuro-ophthalmology. *Can J Ophthalmol.* 2013;48(1):3–7.

Fourth Cranial Nerve Palsy

An acute CN IV palsy typically causes diplopia that is worse in contralateral gaze, ipsilateral head tilt, and downgaze; hence, patients almost always report diplopia (or a tendency to close 1 eye) while reading. In some cases, examination of the affected eye reveals limited downgaze in the adducted position, but in most cases ocular motility appears grossly normal. Accordingly, it is essential to perform PACT or Maddox rod testing to demonstrate a hypertropia that worsens on contralateral gaze and ipsilateral head tilt. Ipsilateral head tilting usually increases the vertical strabismus; thus, patients typically (subconsciously) tilt their head to the opposite side to avoid diplopia.

The *Parks-Bielschowsky 3-step test* is an algorithmic approach to identifying ocular motility patterns that conform to dysfunction of a specific vertically acting extraocular muscle. The 3 steps are as follows:

1. Find the side of the hypertropia in primary gaze.
2. Determine if the hypertropia is greater on left or right gaze.
3. Determine if the hypertropia is greater on left or right head tilt.

Excyclotropia of the affected eye should be assessed by double Maddox rod testing and indirect fundoscopy. The 3-step test is most helpful in determining whether a vertical strabismus conforms to the pattern of a CN IV palsy. For example, a right CN IV palsy shows right hyperdeviation that worsens on left gaze and right head tilt (positive 3-step test) and causes excyclotropia of the right eye. (For more on the 3-step test, see BCSC Section 6, *Pediatric Ophthalmology and Strabismus*.) Occasionally, a skew deviation mimics a CN IV palsy

on the 3-step test. However, in a skew deviation, the hypertropic eye will often be intorted as opposed to extorted, as it is in a CN IV palsy. In addition, moving the patient from sitting to a supine position (by reclining the examination chair) often reduces the magnitude of the hypertropia in skew deviation but has little or no effect on a CN IV palsy. Practically speaking, acquired vertical strabismus not from a CN IV palsy is often the result of the dysfunction of more than 1 muscle and will not generate a positive 3-step test. In particular, TED, myasthenia gravis, or simultaneous dysfunction of multiple CNs can produce a variety of nonspecific patterns of ocular misalignment. The reliability of the 3-step test in identifying patterns of vertical strabismus lessens somewhat over time because of the phenomenon called “spread of comitance” (see the section Comitant and Incomitant Deviations).

Bilateral CN IV palsy should always be considered whenever a unilateral palsy is diagnosed, especially after head trauma. Patients with bilateral CN IV palsy present with

- crossed hypertropia (ie, the right eye is higher on left gaze, and the left eye is higher on right gaze)
- extorsion of $\geq 10^\circ$ (best measured with double Maddox rod testing)
- large (≥ 25 prism diopters [Δ]) V-pattern esotropia
- habitual chin down posture

CN IV palsies are often congenital. Recognized causes of congenital CN IV palsies include an anomalous superior oblique tendon, an anomalous site of its insertion, or a defect in the trochlea. Similarly, some cases of presumed congenital CN IV palsy are secondary to a benign tumor (eg, schwannoma) of the nerve. Patients may be asymptomatic until adulthood, when their vertical fusional amplitudes diminish and diplopia develops. Most patients maintain a chronic head tilt. The longstanding nature of the head tilt may cause facial asymmetry and can often be confirmed by reviewing old photographs (Fig 7-11). Patients with a longstanding CN IV palsy have relatively large vertical fusional amplitudes ($>3 \Delta$). Comparing superior oblique size on MRI between the affected and unaffected sides does not reliably distinguish acquired from congenital palsies.

In patients older than 50 years, an isolated CN IV palsy is typically caused by microvascular ischemia. Function always improves and typically recovers within 6 months.

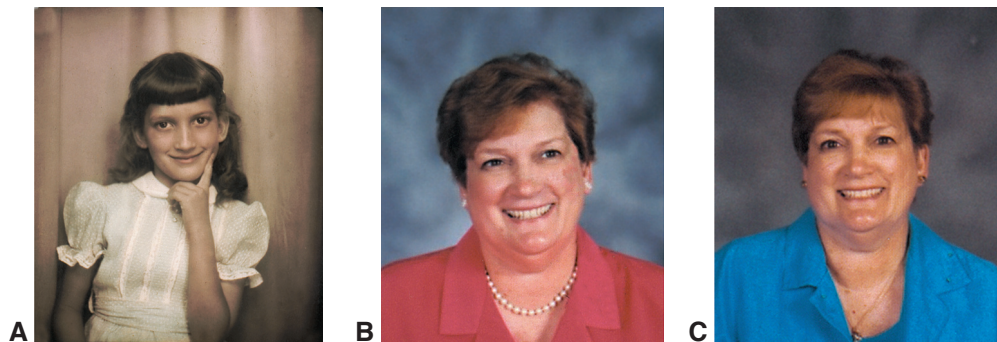


Figure 7-11 Congenital left CN IV palsy. **A**, Note the left hypertropia and right head tilt as a child. **B**, The right head tilt is still present 40 years later, but the patient describes more difficulty maintaining single, binocular vision. **C**, After eye muscle surgery, the diplopia and head tilt have resolved. (Courtesy of Lanning B. Kline, MD.)

CN IV is particularly vulnerable to closed head trauma because of the unique dorsal midbrain-crossing anatomy. In addition, CN IV can be damaged by disease within the subarachnoid space or cavernous sinus.

Diagnostic evaluation for an isolated, nontraumatic CN IV palsy usually yields little information because most cases have congenital, ischemic, or idiopathic causes. In older patients, who are at increased risk for vasculopathy, a full medical evaluation is appropriate to assess for vascular risk factors (eg, diabetes mellitus, hyperlipidemia, and hypertension). Occasionally GCA can cause a CN IV palsy. Older patients should have follow-up evaluation to ensure recovery. Lack of improvement after 3 months should prompt neuroimaging directed toward the skull base to search for a mass lesion. Other possible causes of an acquired vertical strabismus include orbital restrictive syndromes (eg, TED or previous trauma). Skew deviation, partial CN III palsy, or myasthenia gravis should be considered in atypical cases.

Engel JM. Treatment and diagnosis of congenital fourth nerve palsies: an update. *Curr Opin Ophthalmol*. 2015;26(5):353–356.

Helveston EM, Krach D, Plager DA, Ellis FD. A new classification of superior oblique palsy based on congenital variations in the tendon. *Ophthalmology*. 1992;99(10):1609–1615.

Uchiyama E, Matsuo T, Imai S, Itoshima E. Paretic side/normal side ratios of cross-sectional areas of the superior oblique muscle vary largely in idiopathic superior oblique palsy. *Am J Ophthalmol*. 2010;149(3):508–512.

Wong AM, Colpa L, Chandrakumar M. Ability of an upright-supine test to differentiate skew deviation from other vertical strabismus causes. *Arch Ophthalmol*. 2011;129(12):1570–1575.

Sixth Cranial Nerve Palsy

CN VI is the most frequently affected nerve in an isolated ocular motor palsy. CN VI palsy presents as horizontal diplopia that worsens on ipsilateral gaze, correlating with an abduction deficit and esodeviation that increases with gaze to the affected side (Fig 7-12). A pattern of divergence insufficiency or paralysis may occur during the evolving or resolving phase of a CN VI palsy (see Chapter 8).

An ischemic mononeuropathy is the most common cause of an isolated CN VI palsy. Lesions of the *cerebellopontine angle* (especially acoustic neuroma or meningioma) may involve CN VI and other contiguous CNs, causing decreased facial and corneal



Figure 7-12 Left CN VI palsy. **A**, In right gaze, the eyes are aligned. **B**, In straight-ahead gaze, the left eye is inwardly deviated. **C**, In left gaze, the left eye does not abduct, causing a marked misalignment of the eyes. (From Trobe JD. *The Physician's Guide to Eye Care*. 3rd ed. San Francisco: American Academy of Ophthalmology; 2006:118. Image courtesy of W. K. Kellogg Eye Center, University of Michigan.)

sensation (CN V), facial paralysis (CN VII), and decreased hearing with vestibular signs (CN VIII). Chronic inflammation of the petrous bone may cause an ipsilateral abducens palsy and facial pain (*Gradenigo syndrome*), especially in children with recurrent middle ear infections. After exiting the prepontine space, CN VI is vulnerable to meningeal or skull-based processes, such as meningioma, nasopharyngeal carcinoma, chordoma, or chondrosarcoma. In addition, CN VI is susceptible to injury from shearing forces of head trauma or elevated intracranial pressure. In such cases, injury occurs where CN VI enters the cavernous sinus through the *Dorello canal* (the opening below the petroclinoid ligament). The appearance of a CN VI palsy after seemingly minor head trauma should raise concern for a preexisting pathology, such as tumor compression, that makes the nerve more susceptible to injury.

Congenital CN VI palsies almost never occur in isolation. An abduction paresis that is present early in life usually manifests as Duane syndrome (see BCSC Section 6, *Pediatric Ophthalmology and Strabismus*, Chapter 12).

Isolated CN VI palsies in adults older than 50 years are usually ischemic. Ocular motility in such cases usually improves over time and typically resolves within 6 months. Whether or not neuroimaging is required at the time of initial diagnosis is controversial. Some experts recommend neuroimaging at the time of initial presentation. As with other isolated ocular motor cranial nerve palsies, medical evaluation is appropriate. However, a cranial MRI is mandatory if obvious improvement has not occurred after 3 months. Other diagnostic studies that may be required include lumbar puncture, chest imaging, and hematologic studies to identify an underlying systemic process such as syphilis, sarcoidosis, collagen vascular disease, or GCA. Recovery does not necessarily indicate a benign cause. Occasionally, a CN VI palsy will resolve spontaneously and then recur as a manifestation of an intracranial tumor or ocular myasthenia gravis.

Impaired abduction in patients younger than 50 years requires careful scrutiny because few such cases are caused by ischemic cranial neuropathy. Younger patients should undergo appropriate neuroimaging. A CN VI palsy may be the only presenting ocular sign of a posteriorly draining carotid-cavernous fistula (eg, white eye shunt syndrome, discussed later in this chapter). If imaging results are negative, consideration should be given to evaluation for (1) neuromuscular junction disease by obtaining acetylcholine receptor antibody titers or performing edrophonium testing; (2) for mechanical pathophysiologies, such as TED with medial rectus muscle involvement; and (3) for meningeal-based disease by obtaining a lumbar puncture. Leukemia and brainstem glioma are important considerations in children. In adolescents and young adults, demyelination may be the cause, in which case MRI with fluid-attenuated inversion recovery (FLAIR) imaging typically reveals T2 hyperintensities consistent with multiple sclerosis. (See Chapter 2 for a discussion of neuroimaging and Chapter 14 for a discussion of multiple sclerosis.) Other potential CN VI palsy mimics include Duane syndrome (type 1), spasm of near reflex, myasthenia gravis, TED, and medial orbital wall fracture with entrapment.

Tamhankar MA, Bioussé V, Ying GS, et al. Isolated third, fourth, and sixth cranial nerve palsies from presumed microvascular versus other causes: a prospective study. *Ophthalmology*. 2013;120(11):2264–2269.

Ocular Neuromyotonia

Ocular neuromyotonia, a rare but important cause of episodic diplopia, is thought to be neurogenic in origin. Prior skull-based radiation therapy, typically for neoplasm (eg, meningioma), is the most common historical feature. Months to years postradiation, patients experience episodic diplopia lasting typically 30–60 seconds. Ocular neuromyotonia may affect any of the ocular motor nerves or their divisions. Diplopia is often triggered by activation of the affected nerve in eccentric gaze with resultant sustained muscle contraction producing ocular misalignment (eg, CN VI neuromyotonia produces sustained lateral rectus muscle spasm of the involved eye and attendant exotropia). If unrecognized, such patients often undergo extensive and largely unnecessary workup in the search for a recurrent neoplasm. The disorder generally responds well to medical therapy. Carbamazepine and its derivatives constitute first-line treatment.

Kim SB, Oh SY, Chang MH, Kyung SE. Oculomotor neuromyotonia with lid ptosis on abduction. *J AAPOS*. 2013;17(1):97–99.

Miller NR, Lee AG. Adult-onset acquired oculomotor nerve paresis with cyclic spasms: relationship to ocular neuromyotonia. *Am J Ophthalmol*. 2004;137(1):70–76.

Paresis of More Than One Cranial Nerve

The framework for managing isolated ocular motor CN palsies presented earlier in this chapter assumes that no other neurologic abnormalities are present. Benign microvascular disease rarely causes simultaneous involvement of more than 1 ocular motor CN. Simultaneous involvement of unilateral CNs III, IV, V, and VI, and sympathetic nerves strongly suggests a lesion of the cavernous sinus (see the following section). Bilateral involvement of the CNs suggests a diffuse process such as infiltrative disease (eg, carcinoma, leukemia, or lymphoma), a midline mass lesion that extends bilaterally (eg, chordoma, chondrosarcoma, or nasopharyngeal carcinoma), a meningeal-based process, an inflammatory polyneuropathy (eg, Guillain-Barré syndrome or its variant, the Miller Fisher syndrome, or sarcoidosis), or myasthenia gravis.

If symptoms or signs indicate that more than 1 CN is involved, a neurologic evaluation should be undertaken. If neuroimaging is normal, a lumbar puncture with cytopathologic examination should be considered. Special testing for cancer-associated protein markers may be helpful in uncovering an elusive diagnosis. In suspected neoplastic meningeal involvement (ie, meningeal carcinomatosis), combined computed tomography–positron emission tomography (CT-PET) scans are often the studies of choice to demonstrate accessible biopsy sites. Repeat studies may be needed to obtain a definitive diagnosis. *Idiopathic multiple cranial neuropathy syndrome* should be considered only after neuroimaging, cerebrospinal fluid analysis, other tests, and extended observation have excluded neoplastic, inflammatory, or infectious causes.

Cavernous Sinus and Superior Orbital Fissure Involvement

Ipsilateral CN dysfunction involving a combination of CNs III, IV, V, and VI, and sympathetic fibers is the hallmark of ophthalmoplegia that is secondary to a cavernous sinus lesion (see Chapter 1 for illustrations). The presence of CN V involvement with facial

hypoesthesia, a third-order (postganglionic) Horner syndrome, or both is helpful for localizing the lesion to the cavernous sinus. If only 1 CN is involved, it is usually CN VI, which is the only CN not protected within the lateral dural wall of the cavernous sinus. Aggressive lesions of the cavernous sinus, especially infectious or inflammatory processes, may compromise venous outflow and produce engorgement of ocular surface vessels, orbital venous congestion, increased intraocular pressure, and increased ocular pulse pressure.

It is often impossible to distinguish cavernous sinus lesions clinically from those involving the superior orbital fissure. The CNs pass through this fissure from the cavernous sinus into the orbit, and lesions often cross this anatomical boundary. In recognition of this difficulty, the more general designation of *sphenocavernous syndrome* or *parasellar syndrome* may be used. The offending lesion may extend toward the optic canal or into the orbital apex, in which case optic nerve function can be compromised. The designation *orbital apex syndrome* is then applied.

Tolosa-Hunt syndrome

Tolosa-Hunt syndrome is an idiopathic, sterile inflammation that primarily affects the cavernous sinus. Severe, “boring” pain is almost always present. Neuroimaging may show an enhancing mass within the cavernous sinus. The pain typically responds rapidly and dramatically to corticosteroid therapy, but a positive therapeutic response may also occur with neoplastic mass lesions, especially lymphoma. Frequently, it is later discovered that the cause of the painful ophthalmoplegia in patients initially diagnosed with Tolosa-Hunt syndrome is neoplastic. Therefore, Tolosa-Hunt syndrome is a *diagnosis of exclusion*. Other causes of cavernous sinus lesions include aneurysm, meningioma, lymphoma, schwannoma, pituitary adenoma (with or without apoplexy), carotid-cavernous fistula, metastasis, sarcoidosis, and cavernous sinus thrombosis.

Hao R, He Y, Zhang H, Zhang W, Li X, Ke Y. The evaluation of ICHD-3 beta diagnostic criteria for Tolosa-Hunt syndrome: a study of 22 cases of Tolosa-Hunt syndrome. *Neurol Sci.* 2015;36(6):899–905.

Hung CH, Chang KH, Chen YL, et al. Clinical and radiological findings suggesting disorders other than Tolosa-Hunt syndrome among ophthalmoplegic patients: a retrospective analysis. *Headache.* 2015;55(2):252–264.

Kline LB, Hoyt WF. The Tolosa-Hunt syndrome. *J Neurol Neurosurg Psychiatry.* 2001;71(5):577–582.

Carotid-cavernous sinus fistula

Abnormal connections between the cavernous sinus and the carotid artery or its branches introduce high arterial pressure into the normally low-pressure venous circulation of the cavernous sinus. Such a high-pressure connection may reverse blood flow within the superior ophthalmic vein and produce venous congestion within the orbit. Arterialization of conjunctival vessels is a classic sign of this fistula (Fig 7-13). Patients with this condition may have either direct, high-flow connections between the internal carotid artery and the cavernous sinus or indirect, “dural,” low-flow connections mediated by small arterial feeders off the internal or external carotids (Fig 7-14). High-flow, direct fistulas most commonly occur after severe head trauma and produce a cranial bruit, whereas

low-flow, indirect fistulas most often occur spontaneously, particularly in older women. The sequence of events leading to indirect fistula formation is not known. Physical examination cannot reliably distinguish between high-flow and low-flow fistulas, aside from a cranial bruit that indicates high flow. MRA, CTA, or cerebral angiography is necessary to make the correct diagnosis.

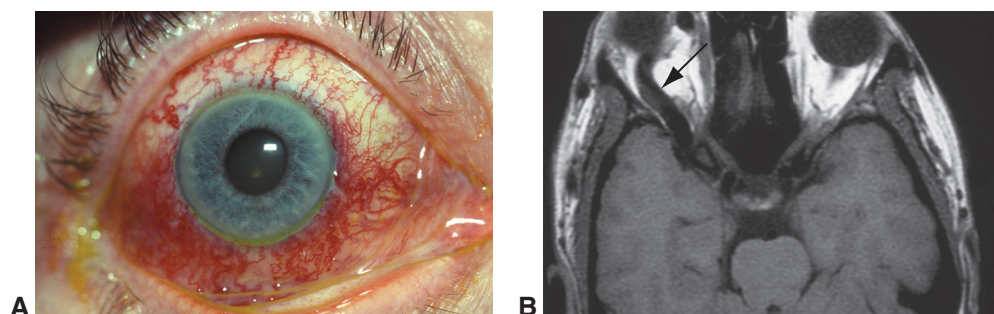


Figure 7-13 Right carotid-cavernous sinus fistula. **A**, The elevated orbital venous pressure produces enlarged, corkscrew, arterIALIZED conjunctival blood vessels that extend to the limbus. **B**, T1-weighted, axial MRI scan reveals an enlarged, dilated superior ophthalmic vein (*arrow*). (Courtesy of Karl C. Golnik, MD.)

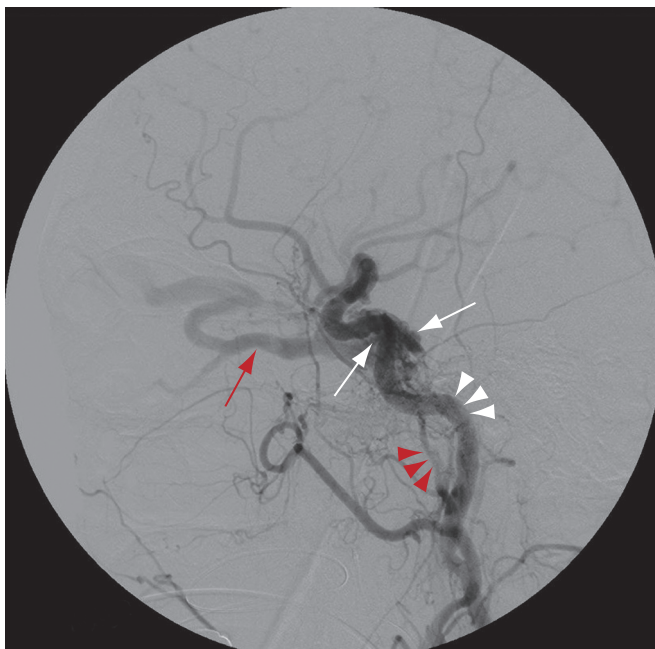


Figure 7-14 Lateral cerebral angiogram with right common carotid artery injection. Note cavernous sinus fistula (ill-defined area, *white arrows*) filling from both the external branches (*red arrowheads*) and internal branches (*white arrowheads*). The superior ophthalmic vein (*red arrow*) is markedly enlarged and fills inappropriately during the early arterial phase of this study, consistent with a carotid-cavernous sinus fistula. (Courtesy of Prem S. Subramanian, MD, PhD.)

Direct and indirect carotid-cavernous sinus fistulas often produce elevated intraocular pressure and proptosis but may also cause the following signs or symptoms:

- diplopia resulting from either cranial nerve palsy or orbital congestion
- arterial or venous compromise to the retina and eye
- ischemic optic neuropathy
- choroidal effusions (Fig 7-15)
- ocular pain (which may partly result from ocular surface drying if proptosis is significant)
- cerebral venous infarction (rare) resulting from venous hypertension

Compression of CN VI due to a posteriorly draining fistula can cause an isolated CN VI palsy. Patients should be asked about pulsatile tinnitus, which is often present. Some indirect fistulas remain stable or close spontaneously; however, both types of fistulas may be successfully treated with interventional radiologic techniques or radiosurgery. Angiographic studies are required to determine the location and configuration of

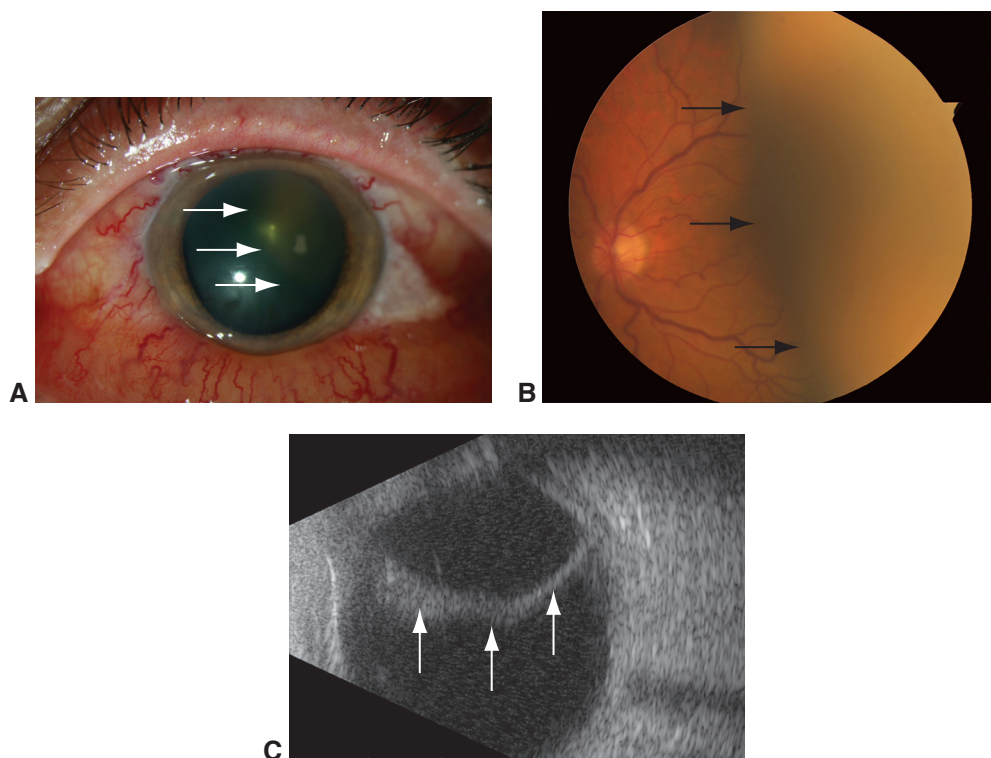


Figure 7-15 Choroidal effusion due to carotid-cavernous fistula. **A**, Slit-lamp photograph of left eye showing chemosis and arteriolarization of conjunctival vessels from a left carotid-cavernous fistula (arrows point to the shadow corresponding to choroidal effusion). **B**, Fundus photograph of left eye showing macular-involving choroidal effusion (arrows). **C**, B-scan demonstrating choroidal effusion (arrows). (Parts A and B courtesy of Zoë R. Williams, MD; part C courtesy of David A. DiLoreto Jr, MD, PhD.)

the fistula, and a variety of thrombogenic materials (eg, coils, beads, or balloons) may be employed to eliminate the abnormal vascular flow.

Subramanian PS, Williams ZR. Arteriovenous malformations and carotid-cavernous fistulae. *Int Ophthalmol Clin*. 2009;49(3):81–102.

Neuromuscular Junction Causes of Diplopia

The prototypical disease of the neuromuscular junction is myasthenia gravis. It typically produces variable diplopia and ptosis with any pattern of pupil-sparing, painless ocular misalignment. Conversely, it never produces sensory symptoms, pain, or pupillary dysfunction. Accordingly, myasthenia gravis belongs in the differential diagnosis of any such case of diplopia (see Chapter 14).

Myopathic, Restrictive, Orbital, and Other Causes of Diplopia

Eye movements may be restricted by congenital or acquired mechanical factors. Congenitally deficient neural innervation to extraocular muscles can also cause limited eye movements with a restrictive component.

Thyroid Eye Disease

The most common cause of restrictive strabismus in adults is TED. Any of the extraocular muscles may be involved, but the muscles most commonly affected are the inferior and medial recti. When the inferior rectus muscle is involved, an ipsilateral hypotropia typically occurs in primary position that increases in upgaze—the restrictive process pulls the eye down and limits supraduction. When the medial rectus is the affected muscle, an esodeviation typically occurs that increases on lateral gaze to the same side (the enlarged, “tight” medial rectus restricts abduction). The diagnosis of TED is straightforward if associated with proptosis, chemosis, eyelid retraction, and eyelid lag; however, restrictive strabismus may be the only sign. Forced duction testing (see Fig 7-3) may provide information to support this diagnosis. Neuroimaging results for patients with TED typically reveal enlargement of the extraocular muscle bellies with sparing of the tendons (see Chapter 4, Fig 4-16). For a more extensive discussion of TED, see Chapter 4 as well as BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*.

Posttraumatic Restriction

Blowout fractures of the orbit often cause diplopia. The most typical presentation involves fracture of the orbital floor with entrapment of the inferior rectus muscle or its fascial attachments. This entrapment, best illustrated with coronal CT of the orbit, mimics the pattern of vertical strabismus often present in TED. Less commonly, the medial rectus muscle becomes entrapped (see Chapter 2, Fig 2-14). Paretic strabismus from swelling also may occur in the acute phase. In either case, as the swelling resolves, so may the diplopia. Hence, decisions about the need for surgery for orbital blowout fractures must be made judiciously. See also BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*.

Postsurgical Restriction

Binocular diplopia can result from injury to or inflammation within the inferior rectus or other muscles after retrobulbar or peribulbar injection for cataract or other ocular surgery. The onset of vertical diplopia immediately following surgery initially suggests nerve damage or myotoxicity from the local anesthetic. Over time, the initial paretic or myotoxic effect evolves into extraocular muscle fibrosis, leading to an overaction or a restricted eye movement pattern. Consecutively, if the inferior rectus muscle is affected, the involved eye transitions from hypertropic (paretic) to hypotropic (restricted) status. In addition, restrictive diplopia may be caused by pterygium excision, scleral buckle placement, episcleral plaque brachytherapy, or tube shunt procedures.

Sener EC, Kiratli H, Gedik S, Sanac AS. Ocular motility disturbances after episcleral plaque brachytherapy for uveal melanoma. *J AAPOS*. 2004;8(1):38–45.

Strouthidis NG, Sobha S, Lanigan L, Hammond CJ. Vertical diplopia following peribulbar anesthesia: the role of hyaluronidase. *J Pediatr Ophthalmol Strabismus*. 2004;41(1):25–30.

Orbital Myositis

Idiopathic inflammation of 1 or more extraocular muscles typically produces ophthalmoplegia and pain, often with conjunctival hyperemia, chemosis, and sometimes proptosis. The pain may be quite intense and is exacerbated by eye movements. If the inflammation is confined to the posterior orbit, the eye may appear to be white and quiet. Results of CT or MRI typically show enlargement of 1 or more of the extraocular muscles with tendon involvement, and the inflammation often extends into the orbital fat (Fig 7-16). Orbital myositis–related pain usually responds to systemic corticosteroid therapy within 24 hours, whereas diplopia may take longer to resolve. Orbital myositis is usually an isolated phenomenon but may be part of a systemic disease such as granulomatosis with polyangiitis (formerly called Wegener granulomatosis), systemic lupus erythematosus, sarcoidosis, immunoglobulin G4–related ophthalmic disease, lymphoma, or, in rare cases, metastatic disease. Extraocular muscle biopsy should be considered in cases of



Figure 7-16 Orbital myositis. Coronal T1-weighted, fat-suppressed, contrast MRI showing enlargement and enhancement of the right superior oblique, right medial rectus, and right inferior rectus muscles. Axial views showed involvement of the tendons. (Courtesy of Zoë R. Williams, MD.)

recurrent orbital myositis with corticosteroid taper. (See also BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*).

Yamamoto M, Hashimoto M, Takahashi H, Shinomura Y. IgG4 disease. *J Neuroophthalmol*. 2014;34(4):393–399.

Chronic Progressive External Ophthalmoplegia

See Chapter 14 for a discussion of this condition.

Neoplastic Involvement

If cancer infiltrates the orbit, especially cancer from the surrounding paranasal sinuses, eye movements may be impaired, either because of extraocular muscle infiltration or involvement of the ocular motor CNs. Relative enophthalmos or associated eyelid “hang-up” on downgaze may accompany the diplopia. Occasionally, extraocular muscles may be metastatic tumor sites.

Brown Syndrome

Brown syndrome is a restrictive ocular motor disorder that produces limited upgaze when the affected eye is in the adducted position. It is usually congenital but can be acquired. Acquired Brown syndrome is typically found in patients with rheumatoid arthritis, idiopathic orbital inflammatory disease, or trauma, including iatrogenic trauma, but in rare cases, it may be a manifestation of a focal neoplastic metastasis to the superior oblique muscle (see BCSC Section 6, *Pediatric Ophthalmology and Strabismus*).

Heavy Eye Syndrome

“Heavy eye syndrome,” also termed strabismus fixus, may result in progressive esotropia and hypotropia in patients with high myopia. The esotropia and hypotropia are associated with limited abduction and supraduction of the eye resulting from the superotemporal shift of the staphylomatous globe posteriorly, with medial displacement of the superior rectus muscle and inferior displacement of the lateral rectus muscle. The intervening connective tissue band also degenerates. Neuroimaging is necessary to confirm the muscle slippage. The preferred initial surgical approach for heavy eye syndrome is bilateral loop myopexy between the superior and lateral rectus muscles in order to restore the normal anatomic configuration, as opposed to medial rectus muscle recession or lateral rectus muscle resection, which can make the deviation worse.

Durnian JM, Maddula S, Marsh IB. Treatment of “heavy eye syndrome” using simple loop myopexy. *J AAPOS*. 2010;14(1):39–41.

Krzizok TH, Schroeder BU. Measurement of recti eye muscle paths by magnetic resonance imaging in highly myopic and normal subjects. *Invest Ophthalmol Vis Sci*. 1999;40(11):2554–2560.

Ranka MP, Steele MA. Esotropia associated with high myopia. *Curr Opin Ophthalmol*. 2015;26(5):362–365.

Tan RJ, Demer JL. Heavy eye syndrome versus sagging eye syndrome in high myopia. *J AAPOS*. 2015;19(6):500–506.

Sagging Eye Syndrome

Sagging eye syndrome, which can be seen in older patients without the prerequisite of myopia, presents with a mild- to moderate-angle esotropia at distance (ie, divergence insufficiency), full lateral gaze, and minimal hypotropia with limited supraduction (see Chapter 8). The lateral rectus–superior rectus band degenerates, with inferior displacement of the lateral rectus muscle, in conjunction with the prolapse of connective tissue superotemporally, but there is no globe prolapse. In addition, patients often experience degenerative changes that can cause deep superior sulci, high lid creases, and ptosis resulting from levator aponeurosis dehiscence. Sagging eye syndrome is the mechanism underlying divergence insufficiency in the elderly. Augmented medial rectus muscle recession is typically successful in correcting the esotropia.

Rutar T, Demer JL. “Heavy eye” syndrome in the absence of high myopia: A connective tissue degeneration in elderly strabismic patients. *J AAPOS*. 2009;13(1):36–44.

Refractive Procedure–Induced Diplopia

In patients with childhood strabismus, diplopia may be induced by refractive procedures that cause a change in fixation preference to the nondominant eye (eg, monovision correction, cataract surgery on an amblyopic eye prior to the dominant eye, or noncycloplegic refraction leading to undercorrected hyperopia and fixation with the amblyopic eye). “Fixation switch diplopia” resolves with appropriate optical correction to reestablish fixation with the dominant eye.

Kushner BJ. Fixation switch diplopia. *Arch Ophthalmol*. 1995;113(7):896–899.

Foveal Displacement Syndrome

Foveal displacement syndrome from macular disease or surgery can result in typically vertical or oblique binocular diplopia that cannot be corrected with use of a prism.

The Patient With Supranuclear Disorders of Ocular Motility

The *efferent visual system*, the anatomy of which is introduced in Chapter 1, controls ocular movements. Like all efferent nervous systems, the ocular motor system consists of supranuclear and infranuclear pathways. The supranuclear pathways originate from multiple locations and innervate the cranial nerve (CN) nuclei. *Prenuclear* is a more accurate term than *supranuclear* because some of these pathways (eg, the vestibular pathways) originate below the CN nuclei. However, the term *supranuclear* is used throughout the literature and will be used in this chapter as well.

The infranuclear pathways originate in the CN nuclei and innervate the extraocular muscles. The distinction between the supranuclear and infranuclear pathways is clinically important because supranuclear disorders almost always affect both eyes similarly, whereas infranuclear disorders affect each eye differently. The patterns of symmetric dysfunction that occur with supranuclear disorders typically do not produce diplopia, although exceptions such as skew deviation exist. Conversely, infranuclear lesions usually do produce diplopia.

Supranuclear pathways include

- premotor and motor regions of the frontal and parietal cortices
- cerebellum
- basal ganglia
- superior colliculi
- thalamus (dorsal lateral geniculate nucleus and pulvinar)
- brainstem centers (paramedian pontine reticular formation [PPRF], neural integrators, and vestibular nuclei)

Infranuclear pathways include

- ocular motor nuclei
- intramedullary segments of the ocular motor nerves
- peripheral segments of the ocular motor nerves (coursing through the subarachnoid space, cavernous sinus, superior orbital fissure, and orbit)
- neuromuscular junction
- extraocular muscles

Fundamental Principles of Ocular Motor Control

In primates, the afferent visual system is broadly designed to achieve 2 fundamental goals: (1) to detect objects and motion in the environment and (2) to provide a high level of spatial resolution for objects that command attention. The entire retina outside the fovea is essentially devoted to the detection of objects. Only the fovea, which occupies a tiny fraction of the total retinal area, provides the fine-quality resolution that allows us to read or to perform highly precise visual motor tasks. Therefore, if one is to discern the fine details of an object, the image of that object must be precisely located on the fovea.

The ocular motor system directs and holds the fovea in alignment with objects of interest. Six supranuclear ocular motor systems have evolved to meet this challenge (Table 8-1):

1. *Ocular fixation system.* Holds the image of a stationary object on the fovea when the head is not moving
2. *Vestibular-ocular system.* Holds the image steady on the fovea during brief head movements
3. *Optokinetic system.* Holds the image on the fovea during sustained head movements
4. *Saccadic system.* Rapidly brings the image of an object of interest onto the fovea
5. *Smooth-pursuit system.* Holds the image of a moving object on the fovea
6. *Vergence system.* Moves the eyes in opposite directions so that an image of an object of interest is simultaneously held on each fovea

These supranuclear systems are controlled by different anatomical pathways that converge at the level of the brainstem to innervate the ocular motor CN nuclei. Their separate origins allow selective disruption of these ocular motor systems by disease processes. Therefore, targeted clinical examination of these systems allows the clinician to identify the affected system and determine the responsible disease process.

Table 8-1 Ocular Motor Tracking Systems

Type	Speed of Eye Movement	Main Function
Ocular fixation system	Fast	Holds image of stationary object steady on fovea by correcting for ocular drift; “refreshes” image on retina to avoid photoreceptor fatigue
Vestibular-ocular system	Slow	Holds retinal image steady during brief head rotation or translation
Optokinetic system	Slow	Holds retinal image steady during sustained head rotation
Saccadic system	Fast	Rapidly brings image of object of interest to the fovea
Smooth-pursuit system	Slow	Holds image of moving object steady on fovea
Vergence system	Slow	Moves eyes in opposite directions so a single image is simultaneously held on each fovea

Leigh RJ, Zee DS. *The Neurology of Eye Movements*. 5th ed. Contemporary Neurology Series. New York: Oxford University Press; 2015.
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Supranuclear Ocular Motor Systems: Function, Anatomy, Clinical Testing, and Disorders of Eye Movements

Clinical examination of the supranuclear systems includes assessment of ocular fixation, vestibular-ocular reflex (VOR), optokinetic nystagmus (OKN), saccadic and pursuit eye movements, and convergence (see Table 8-1). Each of these movements is controlled by dedicated anatomical pathways, the collective goals of which are to direct and maintain the image of a target of interest on the fovea. Methods of assessing each subsystem and signs of malfunction are described in the following sections. A thorough assessment of ocular motility also requires a search for nystagmus (see Chapter 9). Videos of many of the supranuclear ocular motility disorders discussed in this chapter are available at the NOVEL (Neuro-Ophthalmology Virtual Education Library) website at <http://novel.utah.edu>.

Ocular Fixation System

The ocular fixation system holds the image of a stationary object on the fovea when the head is immobile. Eye movement recordings show that the eye is not completely still during ocular fixation; subclinical eye movements prevent attenuation of neuronal responses in the retina. A basic principle of all sensory systems is that any persistent, unchanging stimulus gradually produces an attenuated neural response. This phenomenon explains, for instance, why one does not attend to the constant tactile stimulus of wearing clothing or a wristwatch.

The degradation of image quality that would result if the eye were completely still is countered by *microsaccadic refixation movements*. These eye movements are continuous, very small amplitude (0.1° – 0.2° of visual angle) square waves. The term *square waves* derives from the appearance of eye movement tracings, in which eye movements of equal amplitude and speed to the left and right have a brief intersaccadic interval that produces tracings in the shape of square waves (see Chapter 9). The to-and-fro movements are small enough that the image is maintained within the field of the fovea but large enough to provide a constantly changing image to photoreceptors, thereby enhancing perceptual quality. As is true for most saccadic movements, there is a slight pause (180–200 milliseconds) between movements, known as an *intersaccadic interval*.

The anatomic pathways that control ocular fixation include the dorsolateral prefrontal cortex, the supplementary eye field, the parietal eye field, regions V5 and V5a, the basal ganglia, and the superior colliculi. Clinical evaluation of ocular stability involves observing the patient's ability to fixate on a target when the head and body are held stationary.

Ocular fixation dysfunction

Malfunction of other ocular motor systems may disrupt steady fixation. Saccadic eye movements that disrupt fixation are referred to as *saccadic intrusions* (see Chapter 9). Saccadic intrusions are of brief duration, quite rapid, and in most cases small amplitude. The most common intrusions are *square-wave jerks* (SWJs), which lead the eyes off and then back onto the target with symmetric movements (amplitude of 0.5° – 3° of visual angle). Infrequent SWJs (4–6 per minute) may be observed in patients with normal vision. Frequent SWJs (>15 per minute) are pathologic and occur in patients with *progressive supranuclear palsy* (PSP) or certain cerebellar diseases. They may also be seen in patients who smoke cigarettes. Other examples of saccadic intrusions include ocular flutter and opsoclonus.

Sustained slow eye movements that disrupt fixation characterize nystagmus, which is often caused by an imbalance of vestibular input to the ocular motor nuclei. A continuous slow eye movement that displaces the eye off fixation, followed by a corrective saccade, is referred to as a *jerk nystagmus*. A continuous slow eye movement that oscillates around fixation without a corrective saccade is referred to as a *pendular nystagmus* (see Chapter 9).

Vestibular-Ocular System (Vestibular-Ocular Reflex)

The VOR holds foveal alignment on a target of interest during brief, high-frequency head movements by generating ocular rotations of equal speed, and in the opposite direction, as that of the head movements. VOR responses are driven by the labyrinth, which is composed of 3 semicircular canals and the otoliths (the utricle and saccule). The labyrinth contains hair cells with cilia that project into the endolymph fluid. Head movement causes endolymph flow that deflects cilia on the hair cells, subsequently altering the neurologic activity of CN VIII. The semicircular canals respond to head rotation, and the otoliths respond to linear head movements and static head tilt. Neural activity (excitatory and inhibitory) from these structures passes along the vestibular nerves to synapses in the CN VIII nuclei in the medulla of the brainstem; from there, the activity projects to the ocular motor nuclei (ie, the VOR pathway; see Chapter 1). CN VIII nuclei have many interconnections with the cerebellum that “fine-tune” the VOR.

Each semicircular canal responds to head movements and governs ocular rotations within the same plane as the canal. In addition, each semicircular canal responds in opposite ways to head movements in each direction within the plane of the canal. Thus, the right horizontal semicircular canal stimulates right CN VIII discharge in response to rightward head rotation and inhibits right CN VIII discharge in response to leftward head rotation. Conversely, the left horizontal semicircular canal excites the left CN VIII in response to leftward head rotation and inhibits the left CN VIII in response to rightward head rotation. This arrangement results in a “push–pull” relationship between the paired canals in which stimulation from 1 canal occurs with inhibition from the contralateral, paired canal.

Stimulation from the horizontal semicircular canal projects via the CN VIII nucleus to the contralateral CN VI nucleus, resulting in horizontal ocular rotations away from the side of the canal. For example, stimulating the right horizontal semicircular canal

generates left gaze. Together, the horizontal canals generate horizontal ocular rotations that are equal in speed and opposite in direction to horizontal head rotation. For example, rightward head rotation stimulates the right horizontal semicircular canal (and inhibits the left horizontal semicircular canal) to generate leftward ocular rotations.

The anterior semicircular canals stimulate upgaze (in response to downward head rotation), and the posterior canals stimulate downgaze (in response to upward head rotation). The anterior and posterior canals also stimulate contralateral torsion in response to dynamic ipsilateral head tilt.

Sustained head rotation stimulates the VOR to generate slow-phase ocular movements that are *opposite the direction* of head rotation (to maintain fixation); these alternate with fast-phase, reflexive, refixation saccades *in the direction* of head rotation (VOR nystagmus). The VOR response to sustained head rotation attenuates fairly quickly as the cilia on the hair cells resume their normal position. However, a “velocity storage” mechanism prolongs the VOR for several seconds during sustained head movements. This velocity storage mechanism is generated by interconnections within the CN VIII nuclei (the vestibular commissure) and is fine-tuned and stabilized by connections with the cerebellum.

The otoliths (saccul and utricle) respond to linear head movement and static head tilt. Head tilt stimulates a response that improves ocular orientation with the horizontal plane. Thus, rightward head tilt stimulates the right otolith to generate compensatory elevation and intorsion of the right eye and depression and extorsion of the left eye. Conversely, leftward head tilt stimulates the left otolith to generate compensatory elevation and intorsion of the left eye and depression and extorsion of the right eye.

Examination can readily elicit evidence of VOR dysfunction. Spontaneous nystagmus may be a sign of imbalanced vestibular input, resulting in a slow-phase gaze deviation that disrupts fixation, followed by a corrective saccade. Nystagmus can be detected by observation of the eyes as the patient fixates on a distant target with the head stationary. Subtle small-amplitude nystagmus can be detected by viewing the fundus with a direct ophthalmoscope while looking for repetitive shifts in the position of the optic nerve head. Note that the optic nerve head is behind the center of ocular rotation and will therefore beat in a direction opposite to that of the nystagmus. This test is first performed while the fellow eye is allowed to fixate on a target. Next, the effect of removing visual fixation (achieved by covering the fixating eye) is assessed. Fixation suppresses nystagmus from peripheral vestibular disorders; thus, the onset of nystagmus after removal of visual fixation suggests the presence of an imbalance of the peripheral vestibular system. In contrast, nystagmus from central vestibular disorders is not altered by fixation and will therefore be observed with or without fixation (see Chapter 9).

The VOR gain (ie, the ratio of the amplitude of eye rotation to the amplitude of head rotation) can be assessed clinically with the head thrust maneuver, which requires the clinician to turn the patient's head briskly while the patient fixates on a target. Normally, if the head is rotated 10°, the eyes will rotate exactly 10° in the opposite direction, with equal speed, to maintain foveation of a stationary target. Any imbalance in the VOR gain results in the eyes being dragged off target at the end of the head thrust, followed by a refixation saccade to recapture the target. The horizontal semicircular canals are evaluated by horizontal head rotation. When the head is rotated toward the side of the lesion,

a defective response is observed. For example, rightward head rotation should stimulate the right horizontal semicircular canal to generate leftward ocular rotations of equal speed and amplitude. If a lesion is present in the right horizontal semicircular canal pathway, the eyes will be dragged off target, followed by a leftward, compensatory, refixation saccade. The anterior and posterior semicircular canals can be assessed by vertical head rotations.

VOR gain may also be tested by measuring visual acuity during head rotations (*dynamic visual acuity*). Relatively small horizontal or vertical head rotations at approximately 2 Hz are performed while the patient reads the Snellen chart. In a patient with normal VOR gain, visual acuity will decrease by 1 or 2 lines at most. Abnormal VOR gain will produce a mismatch between the amplitude of the eye and head movements, causing the intended target to drift off the fovea, resulting in a decrease in visual acuity by several lines (typically 4 or more).

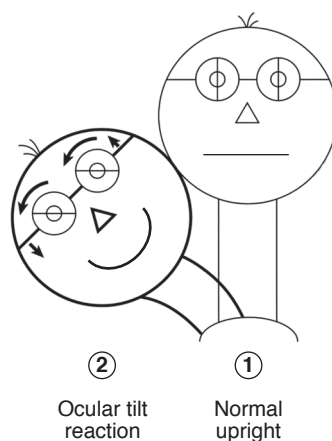
Vestibular-ocular dysfunction

Eye movement abnormalities can develop from either peripheral or central disruptions of vestibular activity, although peripheral end-organ disease of the semicircular canals is by far the most common cause of such abnormalities. Patients with vestibular disease often have nystagmus and abnormal VOR gain (see Chapter 9).

Otolith dysfunction may produce skew deviation or an ocular tilt reaction. *Skew deviation* is a vertical misalignment of the eyes caused by asymmetrical otolithic input to the ocular motor nuclei. The vertical misalignment, which may be comitant or incomitant, may simulate a CN IV palsy, including a positive head tilt test. However, skew deviation typically occurs with intorsion of the hypertropic eye. In contrast, CN IV palsy causes extorsion of the hypertropic eye. Additionally, the vertical deviation in skew deviation typically improves when the patient lies down, whereas it does not change in CN IV palsy. An alternating skew deviation manifests as hypertropia of the abducting eye (ie, right hypertropia on right gaze and left hypertropia on left gaze).

The *ocular tilt reaction*, which occurs with otolithic imbalance, consists of a head tilt, skew deviation, and cyclotorsional rotation of the eyes (Fig 8-1). As described earlier, normally, the otoliths *respond* to head tilt to improve ocular orientation with the

Figure 8-1 Right ocular tilt reaction. To achieve the illusion of normal upright orientation (1), an ocular tilt reaction (2) compensates for the apparent tilt of the environment. With the ocular tilt reaction, the upper poles of each eye rotate toward the lower ear. (Modified with permission from Kline LB, Bajandas FJ. *Neuro-Ophthalmology Review Manual*. 6th ed. Thorofare, NJ: Slack; 2008:71. Modified from Brandt T, Dieterich M. *Pathological eye-hand coordination in roll: tonic ocular tilt reaction in mesencephalic and medullary lesions*. *Brain*. 1987;110(Pt 3):649–666.)



horizontal plane (eg, a right head tilt stimulates the right otolith, resulting in elevation and intorsion of the right eye, and depression and extorsion of the left eye). However, a lesion that decreases innervation from the left otolith (resulting in a pathologic relative increase in innervation from the right otolith) will *drive* the head tilt and generate a left head tilt, elevation and intorsion of the right eye, and depression and extorsion of the left eye (left ocular tilt reaction). The subjective visual vertical may be tilted in the direction of the ocular rotation, although the patient may not recognize that such a shift has occurred.

Skew deviation and the ocular tilt reaction are caused by peripheral or central nervous system (CNS) lesions. A peripheral lesion will generally be ipsilateral to the hypotropic eye (eg, a left otolith lesion is associated with left hypotropic skew deviation or left ocular tilt reaction). However, otolithic innervation crosses within the CNS and projects to multiple ocular motor nuclei, the interstitial nucleus of Cajal, and the cerebellum. Thus, skew deviation and the ocular tilt reaction do not localize dysfunction to a specific region of the CNS and may be caused by lesions anywhere in the brainstem or cerebellum (eg, the posterior fossa) that result in asymmetric otolithic input to the ocular motor nuclei.

Vestibular imbalance is common with lesions of the caudal brainstem (lower pons and medulla) because of disruption to the CN VIII nuclei or their interconnections. One of the better-known stroke syndromes involving this area is the *lateral medullary syndrome* (or *Wallenberg syndrome*). In general, damage to a lateral region of the brainstem disrupts the sensory pathways; therefore, Wallenberg syndrome is a type of “stroke without paralysis” (see Chapter 2, Fig 2-6). Patients may present with the following signs and symptoms:

- ipsilateral loss of facial pain and temperature sensation (involvement of the descending tract of CN V)
- contralateral loss of hemibody pain and temperature sensation (involvement of the lateral spinothalamic tract)
- ipsilateral cerebellar ataxia (damage to spinocerebellar tracts)
- ipsilateral first-order Horner syndrome
- ipsilateral ocular tilt reaction (head tilt toward the side of the lesion)

In addition, patients may have dysarthria, dysphagia, vertigo, or persistent hiccups; there is no extremity weakness.

Although the lateral medulla is in the distribution of the posterior inferior cerebellar artery (PICA), Wallenberg syndrome usually results from occlusion of the more proximal vertebral artery. Consequently, patients may experience *lateropulsion*, the sensation of being pulled toward the side of the lesion, which results from damage to the CN VIII nuclei. Patients may also manifest *ocular lateropulsion*; this effect can be tested by examination of horizontal pursuit and saccadic movements, which will reveal a bias that produces hypermetric movements toward the side of the lesion and hypometric movements away from the side of the lesion. Vertical saccades may follow an elliptical path as the eyes deviate toward the side of the lesion during the vertical movement. Finally, this directional bias also can be observed by noting that the eyes turn toward the side of the lesion after visual fixation is removed for a few seconds.

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- Donahue SP, Lavin PJ, Hamed LM. Tonic ocular tilt reaction simulating a superior oblique palsy: diagnostic confusion with the 3-step test. *Arch Ophthalmol.* 1999;117(3):347–352.
- Wong AM, Colpa L, Chandrakumar M. Ability of an upright-supine test to differentiate skew deviation from other vertical strabismus causes. *Arch Ophthalmol.* 2011;129(12):1570–1575.

Optokinetic System (Optokinetic Nystagmus)

The *optokinetic system* maintains steady alignment of images on the retina during *sustained* rotation of the head (or environment). OKN is induced when a large visual image sweeps across the retina. The initial response is a slow-phase, pursuit-like movement that follows the visual scene, followed by a contraversive, involuntary, reflexive saccade. The VOR generates similar reflexive eye movements. However, the vestibular response is generated by brief head rotations that stimulate the semicircular canals and is attenuated after approximately 30 seconds as the cilia on the hair cells resume their normal position. In contrast, the optokinetic system response is a sustained response that is generated by continuous visual image motion over a large area of retina.

The vestibular and optokinetic systems act synergistically to hold the visual scene steady on the retina during sustained head rotations. For example, when a normal subject is rotated, the VOR initially stimulates the slow-phase ocular rotations in the opposite direction that hold the visual image steady on the retina. However, after approximately 30 seconds, the rotation-induced VOR is attenuated. Thereafter, the optokinetic system responds to the visual scene sweeping across the retina by providing a sustained output, which generates continuous ocular movements that hold the visual image steady on the retina.

The smooth-pursuit system and the optokinetic system are similar but distinct. The smooth-pursuit system is voluntarily activated; its function is to place the image of a small moving object onto the fovea. In contrast, the optokinetic system is involuntary and is reflexively activated when a large visual image sweeps across a large area of retina.

The optokinetic system cannot be isolated for testing in the clinical setting. In order to do so, the moving stimulus would have to fill the complete visual environment. Although practical, OKN induced by the rotating OKN drum of black-and-white stripes that clinicians use in the office subtends only a portion of the visual field and primarily tests the pursuit and saccade systems, not the optokinetic system.

Optokinetic nystagmus dysfunction

Isolating the optokinetic system response from the pursuit response to a moving target requires specialized testing equipment not typically used in the clinical setting. As noted, the OKN drum subtends a small portion of the visual field and therefore primarily tests smooth-pursuit movements in the direction of drum rotation and saccadic eye movements opposite the direction of drum rotation (eg, drum rotation toward the patient's right side generates a rightward ocular pursuit movement followed by a leftward saccade.)

Asymmetry of the OKN drum-induced responses can be caused by a unilateral lesion of the cerebral pathways that descend from the ipsilateral parietal, middle temporal, or

medial superior temporal areas to the brainstem ocular motor centers. These regions control ipsilateral smooth pursuit. Therefore, abnormal, jerky pursuits (ie, saccadic pursuits) will occur when the drum is rotated toward the side of the lesion. Asymmetry of OKN responses, with normal smooth-pursuit movements produced by drum rotation toward the patient's left and abnormal saccadic pursuit movements produced by drum rotation toward the patient's right, suggests a lesion in the right cerebrum. Typically, relatively large lesions of the parietal or parieto-occipital cortex are required to produce drum-induced asymmetries; these lesions are usually accompanied by a homonymous hemianopia. A lesion confined to the occipital lobe (eg, as usually occurs secondary to a stroke within the distribution of the posterior cerebral artery) also produces a homonymous hemianopia but not OKN asymmetry. Thus, the clinician may use the OKN drum to gain insight into the location and extent of a cerebral lesion that produces a homonymous hemianopia.

Saccadic System

The saccadic system rapidly shifts the fovea to targets of interest. Saccades are ballistic, rapid movements that generally cannot be altered once initiated. The speed of saccades correlates with the extent of eye movement; larger-amplitude saccades are faster than smaller-amplitude saccades. This relationship is referred to as the *main sequence*. Saccadic velocity may exceed 500° per second, a speed that allows the eyes to move from primary position to the farthest extent of the temporal visual field in only 0.2 second. Saccadic latency (the interval between appearance of a target and onset of a saccade) is approximately 200 milliseconds, and saccadic duration is generally less than 100 milliseconds.

Saccades may be volitional or reflexive (as in the reflexive quick phases of optokinetic and vestibular nystagmus). Volitional saccades are controlled by several areas of the cerebral cortex, including premotor zones that project to the *frontal eye fields (FEFs)* (see Chapter 1). Descending pathways from the FEFs also communicate with several intermediate structures, including the basal ganglia and superior colliculi. Reflexive saccades are controlled primarily by the superior colliculi. Activation of these pathways generates conjugate, contralateral saccades by innervating the contralateral PPRF. The PPRF contains 2 populations of neurons: (1) *burst cells* that activate the neighboring CN VI nucleus and (2) *omnipause cells* that inhibit the burst cells. The FEFs and superior colliculi generate a saccade by stimulating the burst cells and inhibiting the omnipause cells within the contralateral PPRF. The PPRF burst cells project to the adjacent CN VI nucleus that innervates the ipsilateral lateral rectus muscle and, via the medial longitudinal fasciculus (MLF), the contralateral medial rectus muscle.

The PPRF generates saccades via 2 innervational components: (1) a pulse and (2) a step (Fig 8-2). The *pulse* initiates the saccade with a burst of high-frequency, phasic innervational activity that enables the globe to overcome inertia and the viscous drag of the orbit (gaze initiation). The *step* consists of tonic innervational activity that continues after the saccadic eye movement is complete in order to hold the eye in its new eccentric position against elastic forces in the orbit (gaze holding). The pulse determines saccade velocity, and the step maintains the position of the eye after the saccade. For the saccade to be accurate, the velocity of the saccade (pulse innervation) must match the final

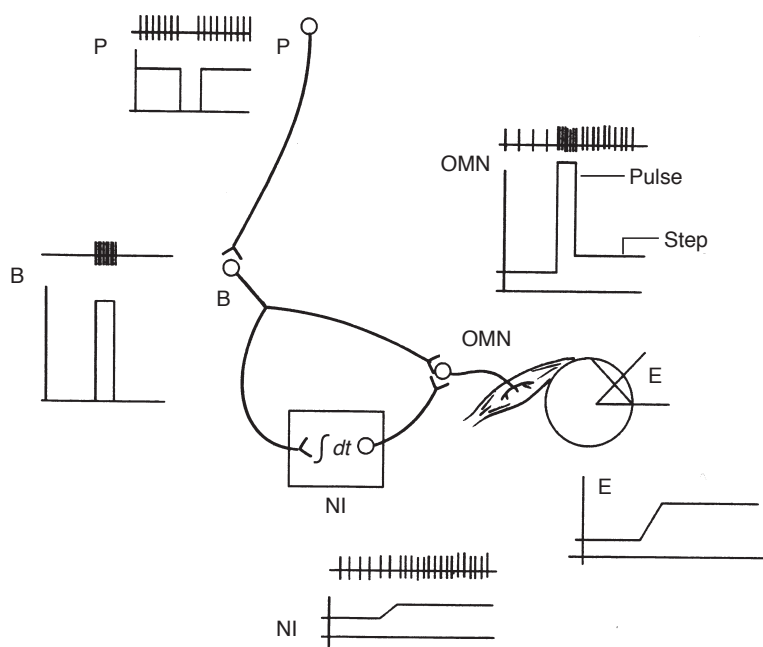


Figure 8-2 Generation of a saccadic eye movement. Omnipause cells (P) cease their discharge just before the onset of a saccade, allowing burst cells (B) to create the pulse that initiates the saccade. The pulse is received by the neural integrator (NI), which determines the appropriate step (dt) needed to maintain the eccentric position of the eyes and modulates the signal to the ocular motoneuron (OMN). The lower-right trace (E) depicts the shift in eye position from baseline to a sustained eccentric position. Vertical lines represent individual discharges of neurons. Underneath each schematized neural (spike) discharge is a plot of discharge rate versus time. (Reproduced with permission from Leigh RJ, Zee DS. *The Neurology of Eye Movements*. 3rd ed. Contemporary Neurology Series. New York: Oxford University Press; 1999.)

ocular position maintained after the saccade is complete (step innervation). The process of matching the pulse and step components of a saccade is referred to as *neural integration*. For horizontal movements, the neural integrator consists of the medial CN VIII nucleus and the accessory nucleus of CN XII (also known as the *nucleus prepositus hypoglossi* [NPH]) in the medulla. The PPRF contains neurons that project directly to the CN VI nucleus as well as neurons that project to the neural integrator prior to innervating the CN VI nucleus, enabling pulse–step integration of horizontal saccades.

The FEFs and the superior colliculi generate volitional and reflexive vertical saccades, respectively, via bilateral descending pathways that project to the *rostral interstitial nucleus of the medial longitudinal fasciculus* (riMLF). The riMLF, which is located in the midbrain, is the supranuclear brainstem center for control of conjugate vertical and torsional saccadic eye movements. Neural integration of vertical saccades occurs in the nearby *interstitial nucleus of Cajal* (INC), which matches phasic pulse innervation (gaze initiation) with tonic step innervation (gaze holding) in order to hold the eyes in the proper vertical eccentric position after completion of the saccade; note that this structure is the homologue of the NPH, which performs the neural integration for control

of horizontal eye movements. Thus, the riMLF contains burst-cell neurons that project directly to the CN III and CN IV nuclei as well as neurons that project to the INC prior to innervating these nuclei, enabling pulse–step integration of vertical saccades.

Saccadic eye movements are fine-tuned by the cerebellum, which receives neural input from the pons and supplies innervation to the PPRF and riMLF. The cerebellum influences saccadic speed and accuracy and assists in neural integration (pulse–step matching).

Volitional saccades can be tested by having the patient rapidly shift gaze between 2 targets, such as the extended index fingers of the clinician's outstretched hands, which are held to the left and right of the patient. Reflexive saccades are tested by observing the quick phases of OKN (elicited by patient fixation on a rotating OKN drum) and vestibular nystagmus (elicited by patient rotation in an examination chair). The *latency* (duration from stimulus to movement), *accuracy* (arrival of the eyes on target), *velocity*, and *conjugacy* (degree to which the 2 eyes move together) of the movements should be monitored. A *hypometric saccade* falls short of the intended target; 1–2 small catch-up saccades may be within normal limits. A *hypermetric saccade* overshoots the target and is usually pathologic.

Saccadic dysfunction

Saccadic disorders may produce involuntary saccades, reduced speed of saccades, poor accuracy of saccades (ie, hypometria or hypermetria), delayed latency to initiate saccades, or the inability to maintain eccentric gaze after completion of a saccade. The specific saccadic disorder relates to the pattern of neural activity delivered to the ocular motor nuclei. Excessive firing of burst cells (or excessive inhibition of omnipause cells) in the PPRF will cause unwanted, involuntary saccadic intrusions that disrupt fixation (see the section “Ocular fixation dysfunction” earlier in this chapter, and Chapter 9).

When a patient appears unable to initiate saccades, the doll's head maneuver can determine whether this inability is the result of a supranuclear or nuclear/infranuclear lesion. In a patient with a supranuclear lesion that causes a horizontal saccadic gaze deficit, the doll's head maneuver will activate the intact vestibular-ocular system, bypassing the PPRF and directly stimulating the CN VI nucleus to induce horizontal gaze. Conversely, a CN VI nuclear lesion will impair horizontal gaze in response to the doll's head maneuver as well as attempted volitional saccades.

Slow saccades can result from central or peripheral lesions (including nuclear and infranuclear lesions). Peripheral lesions almost always produce slowed saccadic movements that are hypometric. In contrast, slow saccades with normal amplitude are typically due to CNS lesions, especially lesions of the cerebral hemispheres or basal ganglia. Irrespective of the location of a CNS lesion, slowed saccades ultimately result from decreased discharge frequency of burst-cell neurons causing a deficit in phasic innervation (the pulse component) of the saccade. Saccadic slowness confined to the horizontal plane suggests dysfunction of the PPRF in the pons, whereas saccadic slowness confined to the vertical plane suggests dysfunction of the riMLF in the midbrain. Patients with PSP have slow volitional saccades, especially in the vertical plane, but their reflexive saccades (the fast phases of OKN) often are initially normal. Other CNS disorders that cause slow saccades include cerebellar degeneration, Huntington disease, Wilson disease, and Whipple disease. Most of these cases typically include a prolonged latency to initiate saccades. Myasthenia gravis

may produce faster-than-normal (“lightning-like”) saccades that suddenly stop short of the intended target (reduced saccadic amplitude).

Dysmetric saccades result from peripheral lesions or from abnormal discharge duration of the burst-cell neurons responsible for phasic innervation (the pulse component) of the saccade. Hypometric saccades can be observed with peripheral or central lesions, whereas hypermetric saccades are usually the result of disease of the cerebellum or its interconnections. The accuracy of saccadic eye movements can be difficult to assess in patients with significant bilateral loss of vision, especially those with large visual field defects (eg, homonymous hemianopia and bitemporal hemianopia). Thus, the clinician should exercise caution in describing the presence of hypometric saccades in these patients.

In other cases, saccades are initiated only after prolonged latency, which is a characteristic feature of ocular motor apraxia (discussed later in this chapter). Assessment of saccadic latency must take into account the patient’s age; a gradual increase in latency may occur with advancing age.

The inability to maintain eccentric gaze after completion of a saccade is a result of decreased tonic innervation (the step component of a saccade). Insufficient tonic innervation arises from infranuclear lesions, cerebellar disease, or malfunction of the neural integrator, often referred to as a leaky integrator (the neural integrator consists of the NPH for horizontal saccades and the INC for vertical saccades). After completion of the saccade, the deficient tonic innervation causes the eyes to drift slowly off of the target back to the central position, followed by a corrective saccade toward the target. This combination of eye movements is known as *gaze-evoked nystagmus* (see Chapter 9).

The most common saccadic dysfunction—the conjugate limitation of upgaze characterized by eye movements that have reduced range but normal velocity—is part of normal aging. Abnormalities of saccadic function are relatively nonspecific with regard to etiology and site of the lesion, but notable exceptions occur in which saccadic abnormalities provide important clues to the diagnosis. These exceptions include

- slowed saccades in a patient with extrapyramidal (ie, Parkinson-like) syndrome with imbalance and impaired cognition, which suggest a diagnosis of PSP
- hypermetric saccades, which usually indicate disease of the cerebellum or its out-flow pathways
- unidirectional hypermetric saccades, ocular lateropulsion, and hypermetric pursuit movements, which are generally present as part of the lateral medullary syndrome (Wallenberg syndrome)

Ocular motor apraxia An extreme instance of saccadic dysfunction is ocular motor apraxia. An *apraxia* is an inability to voluntarily initiate a movement that can be initiated by another means, which reveals that a paralysis is not present.

Ocular motor apraxia in children is characterized by increased latency or failure of saccadic initiation. Voluntary and reflexive saccades (in response to OKN and VOR) are affected. Horizontal OKN drum rotation induces lateral gaze in the direction of drum rotation, as slow-phase pursuit movements are relatively intact. However, the failure to generate saccades consistently results in the eyes getting “locked up” in lateral gaze. Saccades, once generated, are often hypometric.

Congenital ocular motor apraxia (as described by Cogan) is idiopathic and is characterized by increased latency and intermittent failure of horizontal saccadic initiation. Vertical eye movements are normal. Children with congenital ocular motor apraxia characteristically use horizontal head thrusts past the point of interest, employing the VOR to move the eyes into extreme contraversion until foveation on the target is possible; this maneuver is followed by slower head rotation in the opposite direction to primary position while the eyes maintain target fixation. Older patients use subtle head movements and blinking to generate saccades. Infants with congenital ocular motor apraxia may be misperceived as having poor vision because they cannot initiate saccades to fixate objects, and they do not yet have the head control to utilize head thrusts.

The location of the lesion that causes congenital ocular motor apraxia is not known. Saccades, once initiated, are of normal velocity and often hypometric; however, normal-velocity, large-amplitude saccades are occasionally generated, indicating that the burst-cell neurons are intact and that the lesion is therefore proximal to the PPRF. Patients with this condition may have other neurologic abnormalities, including mild developmental delay. Neuroimaging may be normal, although multiple abnormalities of uncertain significance, most commonly cerebellar vermis hypoplasia, have been described. Most cases are sporadic, although familial inheritance (autosomal dominant and recessive) has been reported.

Ocular motor apraxia in children is associated with several diseases, including ataxia telangiectasia, Joubert syndrome, Pelizaeus-Merzbacher disease, Niemann-Pick disease type C, Gaucher disease, Tay-Sachs disease, abetalipoproteinemia (which causes vitamin E deficiency), and Wilson disease. In these cases, both vertical and horizontal saccades are affected. Head thrusting is present in approximately half of these cases. Other signs that should prompt a search for an associated disease include nystagmus, skew deviation, retinal pigment epithelial changes, ataxia, seizures, and progressive developmental delay. If these signs are present, a workup should include neuroimaging, an electroretinogram, and genetic evaluation.

Acquired ocular motor apraxia in adults results from bilateral lesions of the supranuclear gaze pathways of the frontal and parietal lobes, usually caused by bilateral strokes, often as part of an anoxic encephalopathy following either cardiac arrest or coronary artery bypass grafting. This condition has also been observed after thoracic aortic aneurysm repair. Patients are unable to initiate voluntary saccades (horizontal and vertical) and often blink to break the fixation and then turn their head toward a new point of interest. Reflexive saccades are intact. Bilateral lesions at the parieto-occipital junction may impair the guidance of volitional saccades. Such inaccurate saccades, together with *optic ataxia* (inaccurate arm pointing; eg, when a patient misdirects his or her hand when attempting to shake yours, despite being able to see your hand) and *simultanagnosia* (disordered visual attention that makes it difficult for a patient to perceive all the major features of a scene at once) are known as *Balint syndrome*; this syndrome is often associated with cognitive dysfunction (see Chapter 6).

Cogan DG. Congenital ocular motor apraxia. *Can J Ophthalmol.* 1966;1(4):253–260.

Harris CM, Shawkat F, Russell-Eggitt I, Wilson J, Taylor D. Intermittent horizontal saccade failure ('ocular motor apraxia') in children. *Br J Ophthalmol.* 1996;80:151–158.

Smooth-Pursuit System

The smooth-pursuit system generates smooth conjugate eye movements that maintain the image of a moving target on the fovea. Pursuit eye movements are able to track a moving target both when the head is immobile and when it is in motion. In order to perform the latter function, the pursuit system must override the VOR. For example, rightward head rotation stimulates the VOR to move the eyes in the opposite direction, toward the left. Therefore, in order to track a rightward-moving object with simultaneous rightward head rotation, the pursuit system (which tracks the object by moving the eyes toward the right) must cancel the VOR (which drives the eyes in the opposite direction, toward the left).

Pursuit movements cannot be generated without a moving target; attempts to pursue an imaginary target will result in a series of saccades. When a patient tracks an object, the moving target generates signals from the M ganglion cells in the retina that are relayed through the magnocellular layers of the lateral geniculate nucleus to the striate cortex (V1), and from there to the extrastriate cortex (V2, V3). These signals are subsequently relayed to the middle temporal (MT) area (where neurons preferentially respond to the speed and direction of moving stimuli), the medial superior temporal (MST) area, the posterior parietal cortex, and the FEF. The MT and MST areas are part of the *dorsal visual processing stream*, which plays an important role in detecting moving visual stimuli (see Chapter 1, Fig 1-23). The descending cortical pathways of the temporal, parietal, and frontal lobes converge and pass through the posterior limb of the internal capsule to innervate the ipsilateral dorsal lateral pontine nucleus (DLPN). The pathway that follows the DLPN comprises 2 decussations. First, the neurons in the DLPN decussate and project to the contralateral cerebellar lobe (the first decussation), which in turn innervates the medial CN VIII nucleus. Thereafter, neurons in the medial vestibular nucleus decussate and project to the contralateral CN VI nucleus (the second decussation). The CN VI nucleus initiates conjugate horizontal eye movements by innervating the ipsilateral lateral rectus muscle and, via internuclear neurons that travel in the MLF, the contralateral medial rectus muscle. Thus, the cortical regions control ipsilateral pursuit movements as a result of the double decussation pathway. Vertical pursuit movements are generated by similar pathways that ultimately stimulate CN III and CN IV.

Clinicians test pursuit eye movements by having the patient's eyes follow a predictably slow-moving target horizontally and then vertically while the head and body are held in position. Two main types of pursuit dysfunction occur: (1) abnormal gain and (2) delayed initiation. The gain of pursuit eye movements should be 1—that is, the eyes should accurately follow the slow-moving stimulus. A low gain results in eye movements that trail the target (ie, the motor output is not commensurate with the speed of the moving target), which prompts initiation of catch-up saccades to maintain visual fixation. This combination of too-slow pursuit movements with interposed saccades is called *cogwheel*, or *saccadic pursuit*. Conversely, a high gain causes the eyes to pursue ahead of the target, which prompts backup saccades.

The OKN drum can be used to evaluate smooth pursuit. The smooth-pursuit system generates the eye movements that follow the rotating lines on the OKN drum. Pursuit movements toward the side of drum rotation should be accurate without saccadic

interruptions. The OKN drum should be rotated to each side to evaluate the symmetry of the pursuit response.

The smooth-pursuit system can also be evaluated by testing VOR cancellation. This is assessed by having the patient fixate on a target (his thumb or a near card) in his outstretched hand while he is rotated from side to side in the examination chair. The patient's head, the target, and the chair rotate in the same direction as a unit. If the smooth-pursuit system cancels the VOR, the patient will maintain fixation on the target during chair rotation. If the smooth-pursuit system does not cancel the VOR, the VOR will drive the eyes off target in the direction opposite of the chair rotation, followed by a corrective saccade. For example, a patient with intact VOR cancellation will maintain fixation on his thumb during rightward chair rotation. If there is inadequate VOR cancellation, the VOR will rotate the eyes off of the thumb to the left in response to rightward rotation. This will be followed by a rightward corrective saccade, which indicates low pursuit gain to the right (Fig 8-3). It is normal in such assessments for the patient to exhibit catch-up saccades during the first 4 or 5 rotations but not thereafter.

Smooth-pursuit system dysfunction

Smooth-pursuit system dysfunction is of poor localizing value. Accompanying neurological abnormalities are often required to determine the location and etiology of the lesion.

Abnormal gain is typically observed in older patients without other definable neurologic problems or secondary to use of a wide range of medications. With age, reduced gain decreases the smoothness of smooth pursuit, although obvious saccadic pursuit is pathologic.

Large cerebral lesions that involve the frontal, parietal, or temporal lobe or the underlying white matter may cause decreased pursuit gain (saccadic pursuits) when the patient fixates on an object moving toward the side of the lesion. These lesions may cause an asymmetric OKN response, with abnormal saccadic pursuits in response to drum rotation toward the side of the lesion and normal smooth pursuits when the drum is rotated away from the side of the lesion. Occipital lobe lesions do not cause OKN asymmetry.

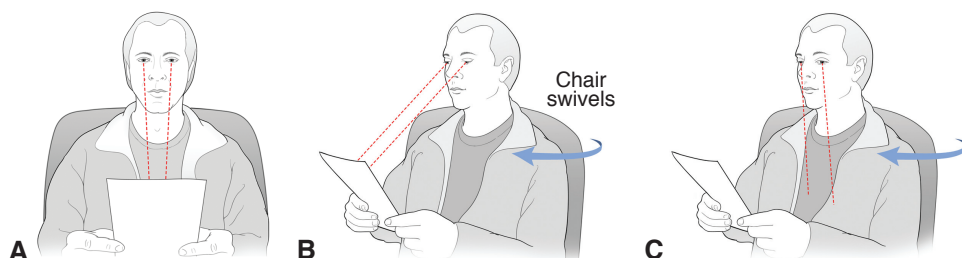


Figure 8-3 Clinical assessment of vestibular ocular reflex (VOR) suppression. **A**, The patient is seated in a swivel chair, fixating on the letters of a near card held at arm's length. **B**, If VOR suppression is normal (intact), the eyes maintain fixation on the target as the chair, the patient's head and arms, and the card rotate together as a unit. **C**, Conversely, if VOR suppression is impaired, the eyes are dragged off target during rotation due to an inability to cancel the VOR. In this example, the chair is rotated to the patient's right, and the VOR moves the eyes to the patient's left, prompting a rightward saccade to regain the target; this result likely indicates right cerebellar system pathology. (Illustration by Christine Galapp.)

Cerebellar disease of any etiology may cause saccadic pursuits and an inability to cancel the VOR, demonstrated by the chair rotation fixation test (see Fig 8-3). Accompanying signs of cerebellar disease are often present.

Smooth-pursuit deficits are usually present in both horizontal and vertical planes, although the vertical plane may be involved selectively in patients with bilateral *internuclear ophthalmoplegia* or PSP.

Vergence System

Vergence eye movements slowly drive the eyes in opposite directions to maintain the image of an object on the fovea of both eyes as the object moves toward or away from the observer. Vergence stimuli include tonic vergence, fusional vergence, accommodative vergence, and voluntary vergence. Without innervation, the anatomy of the orbits creates a divergent misalignment of the eyes (as occurs during sleep or anesthesia). Thus, a baseline amount of *tonic vergence* is required to align the eyes in alert humans. *Fusional vergence* is driven by a disparity in the relative location of images on the retinas and realigns the lines of sight to achieve single binocular vision. *Accommodative vergence* is driven by retinal blur. As an object approaches the eye, retinal blur stimulates the near triad, which consists of accommodation, convergence, and pupillary constriction. Humans are also able to voluntarily stimulate the near triad (*voluntary vergence*). Clinically, the most important stimuli for vergence consist of retinal disparity (*fusional vergence*) and retinal blur (*accommodative convergence*, as part of the near triad).

The cerebral structures controlling vergence movements in primates are not well understood. Binocularly driven cortical cells in the occipital lobe as well as regions of the frontal, parietal, and temporal lobes innervate brainstem neurons located in the mesencephalic reticular formation just dorsal to the CN III nuclei (both directly and via the cerebellum). The mesencephalic reticular formation in turn innervates the medial rectus subnucleus of each CN III nucleus, resulting in convergence.

Convergence is tested with an accommodative target that has enough detail to require an effort to see it clearly (a penlight or finger is not adequate). Fusional and accommodative convergences are simultaneously evaluated by determining the near point of convergence (NPC). The patient fixates on a small accommodative target that is slowly brought toward the nose. The NPC is the distance at which fusion is not maintained and a divergent movement occurs. A normal NPC is approximately 3–5 cm from the nose.

Fusional convergence is measured by placing a *base-out prism* in front of 1 eye while the patient fixates on a target, either near or at a distance. The prism strength is increased until diplopia occurs (ie, until fusion is broken). The strength of the prism at which diplopia occurs is the convergence amplitude. Divergence amplitudes are measured in a similar manner with *base-in prisms*. Normal convergence amplitudes are 25 prism diopters (Δ) for distance fixation and 35 Δ for near fixation.

Accommodative convergence is measured by the accommodative convergence/accommodation ratio (AC/A ratio), using the *lens gradient method* or the *heterophoria method*. The lens gradient method entails performing the prism and alternate cover test to measure the ocular deviation with distance fixation. The test is repeated with a -2.00 D lens placed in front of each eye. The change in the ocular deviation after lens placement

(in prism diopters) is divided by 2 to determine the AC/A ratio. A normal AC/A ratio is 3–5 Δ /D. The *heterophoria method* determines the AC/A ratio by the following formula:

$$AC/A = \text{pupillary distance (in centimeters)} + (\text{deviation near} - \text{deviation distance})/3.$$

Vergence dysfunction

Although vergence disorders are common, they can be challenging to diagnose because convergence depends strongly on patient effort. These disorders are frequently classified as convergence insufficiency, accommodative esotropia, convergence spasm, or divergence insufficiency. Unlike other supranuclear disorders, vergence disorders usually result in diplopic symptoms.

Convergence insufficiency Convergence insufficiency (CI) consists of an exodeviation that is greater at near fixation than at distance fixation. It is a common cause of eye strain, headache, blurred vision, and intermittent diplopia during near-point tasks. Patients with CI have decreased convergence amplitudes and a remote NPC, often greater than 10 cm. This condition often occurs as an isolated finding; in the absence of other neurologic symptoms, further workup is not needed. Nonetheless, many neurologic conditions are associated with CI, most notably closed head trauma and extrapyramidal disorders such as Parkinson disease and PSP. Lesions of the pretectal area may also be associated with CI; however, such lesions are typically accompanied by other features of dorsal midbrain syndrome (see the section Gaze Preference, Gaze Palsy, and Tonic Deviations). In rare instances, lesions of the midbrain (within the mesencephalic reticular formation and just dorsal to the CN III nuclei) may cause CI with normal CN III function. Treatment options include monocular occlusion, convergence exercises, prism glasses, and, in rare cases, strabismus surgery.

Accommodative esotropia Excessive convergence tone is typically observed in younger patients who have an inborn convergence abnormality that manifests as an early-onset esotropia—that is, a high AC/A ratio, which produces an excessive amount of convergence for a given amount of accommodation (see BCSC Section 6, *Pediatric Ophthalmology and Strabismus*).

Spasm of the near reflex (convergence spasm) Spasm of the near reflex consists of intermittent episodes of excess convergence, accommodation, and pupillary constriction. Isolated spasm of the near reflex is almost never related to organic disease. However, when convergence spasm is associated with other abnormalities, especially convergence-retraction nystagmus and reduced conjugate upgaze (as in dorsal midbrain syndrome), organic neurologic impairment is present. Acquired convergence spasm may also be observed in patients with lesions at the junction of the diencephalon and mesencephalon, thalamus, lower brainstem, and cerebellum, in association with other signs and symptoms related to lesion location (eg, thalamic esotropia due to thalamic hemorrhage, Wernicke encephalopathy, Arnold-Chiari malformation, multiple sclerosis, midbrain stroke, and phenytoin intoxication).

Divergence insufficiency Divergence insufficiency (DI) is an acquired ocular misalignment defined by an esodeviation that is greater at distance than near fixation, without

lateral incomitance and without abduction deficits. This disorder is usually benign and not related to neurologic dysfunction. In older patients, DI often results from involution of the connective tissue band between the superior rectus and lateral rectus muscles, causing inferior displacement of the lateral rectus muscles (ie, sagging eye syndrome). The malpositioned lateral rectus muscles have reduced abduction force, resulting in DI pattern esotropia. Rarely, DI may be caused by neurological disorders such as increased intracranial pressure, midbrain tumors, Miller Fisher syndrome, head trauma, intracranial hypotension, Arnold-Chiari malformation, and cerebellar degeneration (often with other signs of these disorders). In addition, DI can be confused with bilateral CN VI palsies, incipient unilateral CN VI palsy, or resolving CN VI palsy. Unlike DI, CN VI palsy is associated with slow abduction saccades and abduction deficits. When present as an isolated neurologic finding, DI does not require further workup, although patients should be observed for development of other neurologic signs. Treatment options include monocular occlusion, prism glasses, and strabismus surgery.

Chaudhuri Z, Demer JL. Sagging eye syndrome: connective tissue involution as a cause of horizontal and vertical strabismus in older patients. *JAMA Ophthalmol.* 2013;131(5):619–625.

Jacobson DM. Divergence insufficiency revisited: natural history of idiopathic cases and neurologic associations. *Arch Ophthalmol.* 2000;118(9):1237–1241.

Gaze Preference, Gaze Palsy, and Tonic Deviations

Gaze preference is an acute inability to produce gaze contralateral to the side of a cerebral (supranuclear) lesion; it is accompanied by a tendency for tonic deviation of the eyes toward the side of the lesion. In such cases, the doll's head maneuver generates a full range of horizontal eye movements because the vestibular-ocular pathways are intact. Stroke is the most common etiology for this type of cerebral injury. The eye movement dysfunction is generally temporary, lasting only days or weeks. Presumably, alternative cerebral-bulbar pathways (perhaps from the parietal lobe) become increasingly capable of generating the saccades and maintaining central gaze.

Gaze palsy is a symmetric limitation of the movements of both eyes in the same direction (ie, a conjugate ophthalmoplegia). Brainstem lesions that produce a horizontal gaze palsy disrupt eye movements toward the side of the lesion (opposite to the pattern observed with lesions of the FEF). With CN VI nuclear lesions, a gaze palsy occurs because the CN VI nucleus also contains internuclear neurons destined for the contralateral CN III subnucleus via the MLF. CN VI nuclear lesions damage the final common site for supranuclear innervation of horizontal eye movements; thus, the doll's head maneuver is ineffective in driving the paretic eyes toward the side of the lesion. Bilateral pontine injury can abolish all horizontal eye movements (Fig 8-4). This devastating injury still allows vertical eye movements, which often occur spontaneously (ie, ocular bobbing). Congenital horizontal gaze palsy can occur as part of Möbius syndrome, in which aplasia of the CN VI nuclei is accompanied by bilateral facial paresis.

Vertical gaze palsies can manifest as selective limitation of upgaze or downgaze. In either case, the lesion is usually in the midbrain. Limitation of conjugate upgaze occurs with

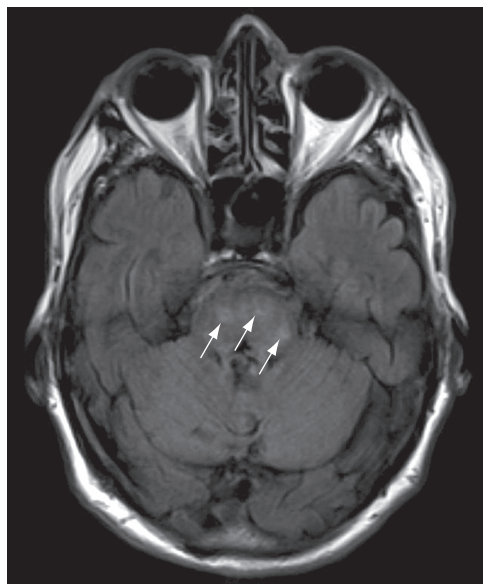


Figure 8-4 Axial magnetic resonance imaging (MRI) scan of a brain. T1-weighted image without contrast shows signal hyperintensity (arrows) in the bilateral pons. This 67-year-old patient reported “trouble moving my eyes” and was found to have a virtually complete horizontal gaze palsy, consistent with ischemia involving the paramedian pontine reticular formation on both sides. She had no other focal neurologic deficits. (Courtesy of Prem S. Subramanian, MD, PhD.)

damage to the pretectum, an isthmus between the superior colliculi and the thalamus. Supranuclear fibers that control vertical gaze (upgaze greater than downgaze) decussate through the pretectum (posterior commissure) as they pass to the riMLF, the midbrain structure that functions as the saccadic generator for vertical eye movements (and thus is the homologue of the PPRF for horizontal saccades). Clinical manifestations of *dorsal midbrain syndrome* (also known as *pretectal* or *Parinaud syndrome*) (Fig 8-5) include

- conjugate limitation of vertical gaze (usually upgaze)
- co-contraction of extraocular muscles with attempted upgaze (convergence-retraction nystagmus)
- mid-dilated pupils with light–near dissociation
- retraction of the eyelids in primary position (*Collier sign*)
- skew deviation
- disruption of convergence (convergence spasm or convergence palsy)
- increased SWJs

Patients with dorsal midbrain syndrome often present with only a subset of these signs, although the limitation of conjugate upgaze is the most common feature. Common etiologies of this syndrome include hydrocephalus, ventriculoperitoneal shunt malfunction, mass lesions (especially pineal-based tumors), multiple sclerosis, stroke, and Whipple disease. Workup must include neuroimaging. Treatment consists of addressing the underlying etiology. Residual diplopia can be treated with prisms, and upgaze deficits can be improved with strabismus surgery.

The pretectum is the terminal structure supplied by the artery of Percheron (small penetrating arteries that arise from the area around the top of the basilar artery; see Chapter 1). Stenosis at the origin of these vessels, disease of the more proximal basilar artery,

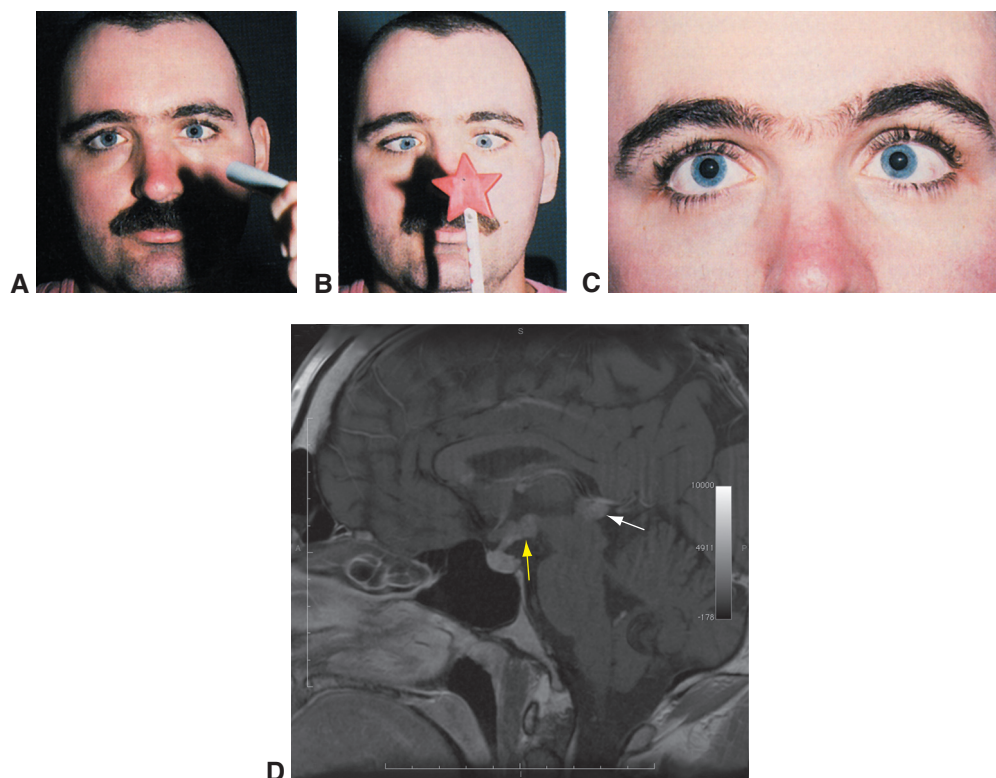


Figure 8-5 Dorsal midbrain syndrome. **A**, A patient with a germinoma pressing on the pretectum shows a poor pupillary light reaction. **B**, The near reaction of the pupils is good. **C**, Attempted upgaze is poorly done. **D**, MRI (T1-weighted with contrast) shows pineal (*white arrow*) and chiasmal (*yellow arrow*) germinoma with involvement of the dorsal midbrain, located beneath the pineal lesion. (Parts A–C used with permission from Albert DM, Jakobiec FA, eds. *Principles and Practice of Ophthalmology*, vol 2. Philadelphia: Saunders; 1994:2476. Part D courtesy of Prem S. Subramanian, MD, PhD.)

or entrapment of emboli that lodge at the top of the basilar artery can infarct the riMLF, resulting in vertical saccadic gaze deficits with relative sparing of vertical pursuit and vestibular-ocular movements.

Deviation of the eyes may occur with seizures involving any cerebral lobe. Most notably, a lesion of the FEF that causes excess neural activity, such as a focal seizure, will drive the eyes contralaterally during the period of the seizure. The head also may turn contralateral to the seizure focus during the ictus. In the postictal state, when there may be lingering hypoactivity of the FEF neurons, the eyes may deviate ipsilateral to the side of the lesion because of a relative increase in input from the unaffected FEF on the opposite side of the brain.

Transient and conjugate downward or upward ocular deviation may occur in healthy newborns. In these cases, the vertical doll's head maneuver can move the eyes out of their tonically held position. Tonic downgaze in premature newborns, however, may be associated with serious neurologic disease, especially when intraventricular hemorrhage expands the third ventricle and presses on the pretectum. Tonic downward deviation of the

eyes combined with retraction of the eyelids, referred to as the *setting sun sign*, is primarily observed in children as part of dorsal midbrain syndrome. Conjugate paresis of upgaze is an associated finding, and in these cases, the doll's head maneuver cannot induce upward movements of the eyes.

Oculogyric crisis is a tonic upward ocular deviation, sometimes directed toward the right or left. Patients find it difficult to direct their eyes downward. This disorder often arises from an idiosyncratic reaction to neuroleptic antipsychotic drugs such as haloperidol and fluphenazine, as well as antiemetic drugs such as metoclopramide, which are strong dopaminergic blockers. These drugs alter supranuclear input onto the ocular motor nuclei. The crisis may persist for hours. Patients with Wilson disease may have an oculogyric crisis. Administration of anticholinergic drugs (eg, prochlorperazine) promptly stops the crisis.

Buckley EG, Holgado S. Surgical treatment of upgaze palsy in Parinaud's syndrome. *J AAPOS*. 2004;8(3):249–253.

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Corbett JJ. Neuro-ophthalmic complications of hydrocephalus and shunting procedures. *Semin Neurol*. 1986;6:111–123.

Keane JR. The pretectal syndrome: 206 patients. *Neurology*. 1990;40(4):684–690.

The Patient With Nystagmus or Spontaneous Eye Movement Disorders

Introduction

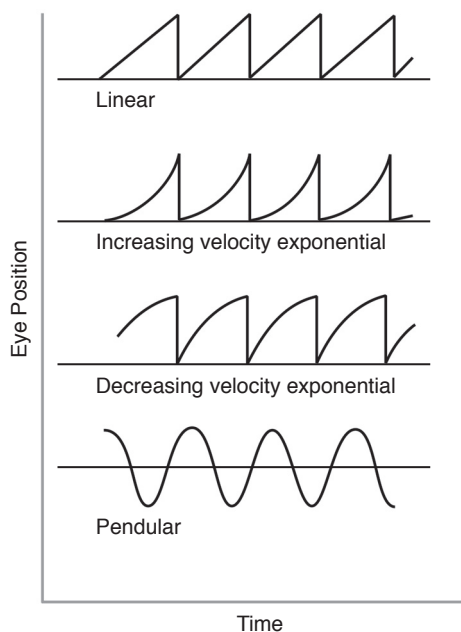
A variety of diseases, drugs, or other factors may disrupt the systems that provide ocular stability. Abnormal eye movements may occur because of inability to maintain fixation, loss of the normal inhibitory influences on eye movement control, or loss of the normally symmetric input from one of the vestibular pathways to the ocular motor nuclei. *Nystagmus* refers to one form of excessive eye movements; this term should be reserved for rhythmic, to-and-fro (eg, horizontal, vertical, torsional, or mixed) eye movements that incorporate a slow phase. *Jerk nystagmus* has 2 phases: (1) a slow-phase drift from the visual target, followed by (2) a corrective saccade (fast phase) back to the target. *Pendular nystagmus* describes back-and-forth, slow-phase movements that occur without a fast phase (Fig 9-1). Abnormal saccadic movements may also drive the eyes off fixation. Collectively, these pathologic eye movements are termed *saccadic intrusions* or *saccadic oscillations*; because they have no slow phase, they do not conform to the definition of nystagmus.

Patients with acquired nystagmus often report *oscillopsia*, a sensation of environmental movement. Children with early-onset nystagmus typically do not have oscillopsia. Nystagmus in primary position may degrade visual acuity. Patients should be asked about any associated neurologic symptoms (eg, vertigo, ataxia, motor weakness, or sensory weakness) and any family history of abnormal eye movements or strabismus.

An examination of ocular motility begins with an assessment of ocular stability in primary gaze. Any abnormal eye movements in the cardinal positions should be examined to determine whether they are

- monocular or binocular
- conjugate (ie, the eyes behave similarly)
- horizontal, vertical, torsional, or mixed in pattern
- continuous or induced by a particular eye position
- characterized by slow phases only (ie, pendular nystagmus), fast and slow phases (ie, jerk nystagmus), or fast phases only (ie, saccadic intrusion)
- reduced at a null point (ie, the field of gaze at which the nystagmus is minimal)

Figure 9-1 Nystagmus waveforms are named for their slow-phase velocity profile. From top to bottom: Linear velocity is typical of vestibular nystagmus; increasing velocity exponential typifies congenital nystagmus; decreasing velocity exponential typifies gaze-evoked nystagmus; and pendular velocity typifies congenital or acquired nystagmus. The horizontal line indicates alignment with the object of fixation. (Modified from Kline LB, Bajandas FJ. Neuro-Ophthalmology Review Manual. 6th ed. Thorofare, NJ: Slack; 2008.)



By convention, the direction of jerk nystagmus is reported as the direction of its fast-phase component; however, it is the slow-phase component that indicates the pathology. *Dissociated* or *disconjugate nystagmus* occurs when the amplitude of oscillations differs in each eye, whereas *disjunctive nystagmus* occurs when the direction of the oscillations differs between the 2 eyes.

The amplitude of nystagmus often changes with gaze position. A few beats of nystagmus are normally present at the extremes of horizontal gaze (beyond 45°), especially in older patients. This finding should not be considered pathologic unless the nystagmus is persistent, asymmetric (eg, present to the left but not the right), or accompanied by other features. Assessment for nystagmus can be complemented by strategies that search for subtler, smaller-amplitude eye movements. Illuminated Frenzel (high-magnification) goggles are extremely useful for detecting eye movements, but a 20.00 diopter (D) lens, slit lamp, or direct ophthalmoscope can also be used to block the patient's fixation and magnify abnormal eye movements. Ocular motor recordings (eg, via electro- or video-oculography, infrared tracking, or electromagnetic scleral search-coil techniques) provide objective and highly sensitive measurements of eye movements but are often unavailable in standard clinical practice. The characteristics of eye movements can be recorded and communicated effectively via drawings and video recordings. Video recordings of many of the forms of nystagmus discussed in this chapter are available at <http://novel.utah.edu>.

In 2001, a National Eye Institute–sponsored committee published a document, “The classification of eye movement abnormalities and strabismus (CEMAS),” which provides a systematic classification of primary eye movement abnormalities and strabismus conditions. Formal definitions of the entities discussed in this chapter can be found in this document.

CEMAS Working Group. A National Eye Institute sponsored workshop and publication on the classification of eye movement abnormalities and strabismus (CEMAS). In: Hertle RW, ed. *The National Eye Institute Publications*. Bethesda, MD: National Eye Institute, National Institutes of Health; 2001.

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Early-Onset (Childhood) Nystagmus

See BCSC Section 6, *Pediatric Ophthalmology and Strabismus*, for additional discussions of early-onset nystagmus.

Infantile Nystagmus Syndrome (Congenital Nystagmus)

Infantile nystagmus syndrome (INS), or congenital nystagmus (CN), is often recognized in the first few months of life but may not become evident until several years of age. There may be a family history of the disorder.

INS is almost always conjugate and horizontal, even in upgaze and downgaze. The nystagmus may be continuous or intermittent and can appear as jerk or pendular movements in different positions of gaze. Eye movement recordings show that these movements are often punctuated by *foveation periods* (brief periods in which the eyes are still and aimed at the object of regard). There is frequently a *null point*, the field of gaze in which nystagmus intensity is minimal and vision during the foveation period is maximized. If the null point is not in primary position, patients often adopt a head turn or posture that places the eyes in the null position in order to improve vision. Visual attention and fixation usually amplify INS (in contrast to peripheral vestibular nystagmus, discussed later in this chapter), whereas convergence on a near target damps the amplitude of the nystagmus. INS is abolished during sleep.

There are 2 characteristic signs of INS:

1. Reversal of the normal pattern of optokinetic nystagmus (OKN). Patients with INS respond to OKN drum rotation with slow-phase eye movements in the direction opposite to that of the rotating OKN drum.
2. A unique pattern in which the velocity of the slow-phase movement increases exponentially with distance from fixation. This increasing-velocity waveform is punctuated by foveation periods. Determining this pattern requires analysis of eye movement recordings (see Fig 9-1).

As mentioned previously, children with INS usually do not have oscillopsia. Visual acuity is determined by the length of the foveation period as well as the accompanying afferent pathway disease, if present. Visual acuity is often reduced, although some patients achieve normal visual acuity. Strabismus occurs in approximately 30% of patients.

INS is associated with conditions that cause bilateral, pregeniculate vision loss prior to 2 years of age. Therefore, the workup of a patient with early-onset nystagmus should

include a search for clinical manifestations of pregeniculate vision loss. In some patients, the etiology may be obvious, such as in children with bilateral, dense, congenital cataracts. However, if the patient's eyes do not have an obvious structural abnormality, the patient should be evaluated for the following conditions, which may be subtle and difficult to detect in uncooperative children:

- *Optic neuropathy.* INS occurs with bilateral optic neuropathies that occur prior to 2 years of age, most commonly optic nerve hypoplasia. The clinician should consider obtaining neuroimaging to detect hydrocephalus or a compressive lesion. The detection of optic nerve hypoplasia requires an endocrinologic evaluation for associated hypopituitarism.
- *Foveal hypoplasia.* INS occurs with foveal hypoplasia, often in patients with albinism or aniridia. Patients should be assessed for other signs of albinism, such as iris transillumination defects and hypopigmentation of the retinal pigment epithelium, choroid, skin, and hair. Albinism and aniridia may be familial.
- *Retinal dystrophy.* INS may occur with early-onset retinal dystrophies such as achromatopsia and Leber congenital amaurosis. Patients should be assessed for other signs of retinal dystrophy, such as photophobia, eye pressing, paradoxical pupils, and high refractive error. Retinal examination may show mild pallor of the optic nerve head and vessel attenuation, or may be normal. The clinician should determine whether the patient has a familial history of retinal dystrophies. Ultimately, electrophysiologic testing (eg, electroretinogram) is required for diagnosis. Children with regression of developmental milestones require further workup for neurometabolic disease.

Approximately 40% of children with typical INS will have no detectable afferent pathway abnormality despite an extensive workup including electrophysiologic testing.

Memantine or gabapentin may reduce the severity of nystagmus and improve visual function in some patients with INS. However, these medications have adverse effects and are not commonly used for childhood nystagmus. The use of base-out prisms to induce convergence may help those patients whose nystagmus damps with convergence. Contact lenses may improve visual function in patients with INS. Some patients with INS can be treated with extraocular muscle surgery (eg, the Anderson-Kestenbaum procedure) to mechanically shift the null point closer to primary position (Fig 9-2; see also Fig 13-3 in BCSC Section 6, *Pediatric Ophthalmology and Strabismus*). A similar procedure may be performed on the vertical recti of a patient with a vertical null point, although diplopia may occur postoperatively because of limited vertical fusional amplitudes. In certain patients, horizontal rectus muscle tenotomy and reattachment of these muscles to their original insertion site may induce a variable reduction in nystagmus amplitude and improve visual function.

Abadi RV, Bjerre A. Motor and sensory characteristics of infantile nystagmus. *Br J Ophthalmol.* 2002;86(10):1152–1160.

Hertle RW, Dell'Osso LF. Clinical and ocular motor analysis of congenital nystagmus in infancy. *J AAPOS.* 1999;3(2):70–79.

Hertle RW; National Eye Institute Sponsored Classification of Eye Movement Abnormalities and Strabismus (CEMAS) Working Group. A next step in naming and classification of eye movement disorders and strabismus. *J AAPOS.* 2002;6(4):201–202.

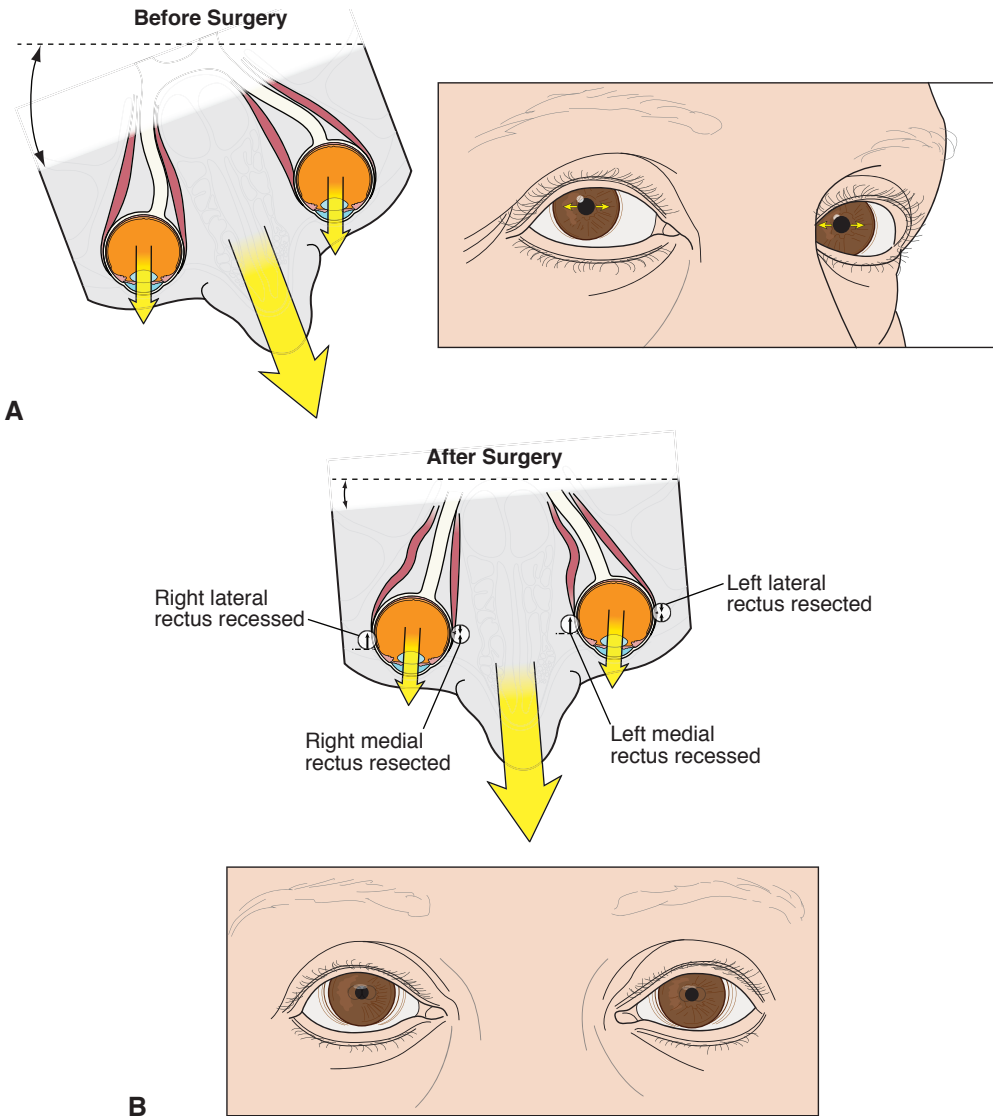


Figure 9-2 Surgical treatment of infantile nystagmus syndrome. **A**, The nystagmus null point is in right gaze (patient maintains left face turn). **B**, The Anderson-Kestenbaum procedure shifts the null point centrally and reduces the head turn. The right lateral rectus and left medial rectus muscles are recessed. The right medial rectus and left lateral rectus muscles are resected. (Illustration by Mark Miller.)

Hertle RW, Dell'Osso LF, FitzGibbon EJ, Thompson D, Yang D, Mellow SD. Horizontal rectus tenotomy in patients with congenital nystagmus: results in 10 adults. *Ophthalmology*. 2003; 110(11):2097–2105.

Fusional Maldevelopment Nystagmus Syndrome (Latent Nystagmus)

Fusional maldevelopment nystagmus (FMN) syndrome, or latent nystagmus (LN), is an early-onset, conjugate, horizontal, jerk nystagmus that is accentuated by monocular

fixation. Eyes with FMN are stable during fusion. However, when 1 eye is occluded (thereby eliminating fusion), the fixating eye slowly drifts toward the nose, followed by a corrective abducting saccade. The eye under the occluder is moving in the same direction and with the same amplitude as the fixating eye (ie, the nystagmus is conjugate). Thus, the fast phase of both eyes beats toward the viewing eye and away from the occluded eye. The fast phase immediately reverses direction upon occlusion of the fixating eye as the fellow eye takes up fixation. Therefore, when a standard occluder is used to measure visual acuity in patients with FMN, acuity is often degraded by the induced nystagmus. Partial optical blurring of 1 eye (with a high-plus lens or filter) may not induce FMN and therefore may permit better visual acuity measurements in the fellow eye.

FMN may occur when both eyes are open if 1 eye is suppressed, a condition termed *manifest latent nystagmus (MLN)*. In other words, the nystagmus is damped with fusion but develops spontaneously whenever suppression occurs; the clinician may not need to occlude an eye to induce this form of nystagmus.

FMN occurs with any condition that disrupts binocular development in the first 6 months of life, most commonly infantile esotropia. Other associated conditions include severe anisometropia, constant infantile exotropia, monocular cataract, corneal opacities, and unilateral microphthalmos. If 1 eye has severe structural damage with poor vision (such as unilateral microphthalmos), then the fellow eye with normal vision will always be the fixating eye and the FMN will always beat toward that eye (because the abnormal eye with poor vision is unable to take up fixation). Patients may maintain a head turn toward the fixating eye. This head posture places the fixating eye in adduction, thereby damping the nystagmus in order to improve vision.

Patients with FMN often have other associated signs of abnormal binocular development, such as dissociated vertical deviation, oblique overaction, and smooth pursuit asymmetry (in which the fixating eye is able to pursue a target moving toward the nose but has difficulty pursuing a target moving away from the nose).

Eye movement recordings show that FMN usually has a constant-velocity or decelerating slow phase, in contrast to the increasing exponential waveform of INS. FMN and INS may coexist.

Dell'Osso LE, Schmidt D, Daroff RB. Latent, manifest latent, and congenital nystagmus. *Arch Ophthalmol*. 1979;97(10):1877-1885.

Heimann-Bielschowsky Phenomenon

Monocular nystagmus in an eye with long-standing poor vision is often referred to as the Heimann-Bielschowsky phenomenon. This phenomenon may occur in patients with poor vision from a variety of underlying etiologies, including optic neuropathy and amblyopia. Onset may occur in adulthood with highly asymmetric vision loss and may not remit even if the visual problem (eg, dense cataract) is corrected. The nystagmus is characterized by intermittent, monocular, vertical, slow, pendular eye movements of low frequency and variable amplitude. Workup is directed toward determining the etiology of the visual loss. The etiology may be obvious on ophthalmologic examination, requiring no additional diagnostic testing (eg, in an infant with unilateral microphthalmos). However,

monocular vertical nystagmus in an infant with a relative afferent pupillary defect and optic nerve head atrophy suggests an optic nerve or chiasmal tumor (glioma) and therefore warrants neuroimaging. Symptomatic oscillopsia is uncommon and can be treated with gabapentin. Strabismus surgery can improve appearance.

Spasmus Nutans Syndrome

Spasmus nutans syndrome is a childhood nystagmus characterized by asymmetric, small-amplitude, high-frequency, “shimmering” eye movements, often accompanied by head nodding and an abnormal head posture (*torticollis*). The nystagmus may be dissociated (sometimes even monocular), and the amplitude and phase relationships of the eye movements may vary between the eyes over the course of a few seconds. The shimmering eye movements are often variable or intermittent; may occur in the horizontal, vertical, or oblique plane; and may increase in the abducted eye during lateral gaze. Head nodding, torticollis, or both occur in approximately 60% of patients and appear to damp the nystagmus and improve vision.

Spasmus nutans syndrome is typically acquired in the first year of life and spontaneously improves 2–8 years later. Secondary amblyopia and strabismus may occur in the more involved eye. The syndrome is sometimes familial and is associated with African American ethnicity, Hispanic ethnicity, and low socioeconomic status.

In general, spasmus nutans syndrome is distinguished from INS by the asymmetric or monocular, high-frequency, small-amplitude, shimmering, multiplanar, variable nature of the nystagmus. In contrast, INS consists of larger amplitude, lower frequency, bilateral, conjugate, symmetric, horizontal, constant ocular movements.

The etiology of spasmus nutans syndrome is unknown. Chiasmal/suprachiasmal tumors (eg, optic pathway gliomas), retinal dystrophies (eg, congenital stationary night blindness), and neurodegenerative disorders (eg, Pelizaeus-Merzbacher disease or Leigh disease) may result in an identical nystagmus. Therefore, neuroimaging is indicated for patients with presumed spasmus nutans syndrome to exclude a glioma of the anterior visual pathway or other parasellar or hypothalamic tumors. An electroretinogram should be obtained if the patient shows signs of a retinal dystrophy (eg, progressive visual loss, photophobia, nyctalopia, eye pressing, paradoxical pupils, or high refractive error). Progressive developmental delay requires an evaluation for neurodegenerative disease.

Patients with spasmus nutans syndrome should be monitored and treated for any associated amblyopia and strabismus. As noted earlier, the abnormal eye and head movements typically disappear after several years (usually by the end of the first decade of life). Lack of resolution or development of other neurologic problems should prompt appropriate evaluation, including neuroimaging.

Kiblinger GD, Wallace BS, Hines M, Siatkowski RM. Spasmus nutans-like nystagmus is often associated with underlying ocular, intracranial, or systemic abnormalities. *J Neuroophthalmol.* 2007;27(2):118–122.

Lambert SR, Newman NJ. Retinal disease masquerading as spasmus nutans. *Neurology.* 1993; 43(8):1607–1609.

Gaze-Evoked Nystagmus

Gaze-evoked nystagmus develops because of an inability to maintain fixation in eccentric gaze. The eyes drift back to the midline as a result of the elastic properties of the orbit, and a corrective saccade is generated to reposition the eyes on the eccentric target. Therefore, the fast phase is always in the direction of gaze. The amplitude of the nystagmus increases as the eyes are moved in the direction of the fast phase. This pattern is in accordance with Alexander's law, which states that nystagmus increases in intensity (amplitude and frequency) as the eyes are moved in the direction of the fast phase.

Gaze-evoked nystagmus is most commonly caused by dysfunction of the *neural integrator* (see Chapters 1 and 8). For horizontal gaze, the neural integrator includes the nucleus prepositus hypoglossi and the medial vestibular nuclei. For vertical gaze, the interstitial nucleus of Cajal serves as the neural integrator. The cerebellum also participates in neural integration of both horizontal and vertical eye movements.

When eccentric gaze is initiated, the neural integrator receives a velocity signal (the *pulse*) from the appropriate gaze center and, through the mathematical process of integration, generates tonic innervation (a *step* signal) to maintain the eccentric position of the eyes after the ocular movements have been completed (see Chapter 8, Fig 8-2). Thus, the neural integrator ensures a level of neural activity adequate to maintain the eyes in an eccentric position of gaze against the elastic forces of the orbit. If the neural integrator fails to function properly (ie, becomes "leaky"), then the tonic innervation (step signal) that holds the eyes in eccentric gaze is deficient. Therefore, after completion of eccentric gaze, the eyes slowly drift off the target back to the central position, followed by a corrective saccade toward the target—hence the term *gaze-evoked nystagmus*.

Pathologic gaze-evoked nystagmus is caused by dysfunction of the structures in the brainstem and cerebellum that participate in neural integration. A few beats of symmetric, low-frequency, small-amplitude jerk nystagmus at the extremes of far horizontal gaze without other ocular motility dysfunction (eg, rebound nystagmus or saccadic dysmetria) constitute physiologic endpoint nystagmus and are not clinically significant. However, sustained, large-amplitude, or asymmetric gaze-evoked nystagmus is pathologic and should prompt further evaluation. The 2 most common etiologies are (1) toxic effects from drugs and medications (eg, alcohol, sedatives, anticonvulsants, and antidepressants) and (2) cerebellar disease. Whenever gaze-evoked nystagmus is asymmetric, an ipsilateral lesion of the brainstem or cerebellum—typically stroke, demyelination, or tumor—is presumably present. Such a finding should prompt appropriate patient evaluation, including targeted neuroimaging. End-organ disease, such as extraocular myopathies and myasthenia gravis, can also cause gaze-evoked nystagmus, with a pattern similar to that observed with lesions of the central nervous system.

Rebound Nystagmus

In some patients with gaze-evoked nystagmus, prolonged eccentric gaze (>30 seconds) reduces the amplitude of the nystagmus. However, when the patient resumes central gaze position, a jerk nystagmus develops in the opposite direction of the initial gaze-evoked

nystagmus, a condition referred to as *rebound nystagmus*. Prolonged eccentric viewing likely induces brainstem/cerebellar compensatory mechanisms that gradually increase tonic innervation toward eccentric gaze, thereby reducing the gaze-evoked nystagmus. When the patient resumes central gaze, residual tonic innervation continues to drive the eyes toward the prior eccentric gaze position, followed by a corrective saccade in the opposite direction (rebound nystagmus). For example, a patient with gaze-evoked nystagmus may have a gradual reduction of the amplitude of a rightward-beating nystagmus with prolonged right gaze because brainstem/cerebellar compensatory mechanisms gradually increase tonic right-gaze innervation. However, upon resuming central gaze, the residual tonic right-gaze innervation continues, inducing a slow-phase ocular rotation toward the right, followed by a corrective, leftward-beating saccade (ie, rightward-beating gaze-evoked nystagmus in right gaze followed by leftward-beating rebound nystagmus upon resuming central gaze). Gaze-evoked nystagmus accompanied by rebound nystagmus is often a manifestation of cerebellar disease.

Vestibular Nystagmus

Peripheral Vestibular Nystagmus

Patients with peripheral vestibular nystagmus typically present with a sudden, sometimes dramatic, onset of disequilibrium with vertigo, nausea, and vomiting (Table 9-1). Patients often recognize that their symptoms are worsened by particular head movements or postures. Oscillopsia, tinnitus, and hearing loss may also occur. After the acute phase of peripheral vestibular loss, which typically lasts days, patients experience a slow period (lasting weeks to months) of gradually waning symptoms. Even patients who become asymptomatic may experience discomfort months to years later when their vestibular system is challenged, for example when riding in a fast-moving car or boat.

Peripheral vestibular nystagmus results from dysfunction of the end organs (eg, semi-circular canals, otolithic structures, or vestibular nerve). End-organ damage is usually unilateral or asymmetric (except in cases of toxicity) and disrupts the normally symmetric

Table 9-1 Clinical Characteristics of Peripheral Vestibular Nystagmus

Clinical Characteristics	Dysfunction
Vertigo	Severe
Tinnitus or hearing loss	Common
Horizontal nystagmus with torsion	Typical
Horizontal nystagmus without torsion	Rare
Pure vertical or torsional nystagmus	Almost never
Duration of symptoms	Days to weeks, improving over time (may be recurrent)
Visual fixation	Damps nystagmus
Common causes	Labyrinthitis, Ménière disease, trauma, toxicity

vestibular afferent input to the ocular motor nuclei. Asymmetric afferent input from the semicircular canals generates vestibular nystagmus. The characteristics of peripheral vestibular nystagmus reflect the combined effects of decreased afferent input from all 3 semicircular canals.

Input from the horizontal semicircular canal is routed to the contralateral abducens nucleus (see Chapters 1 and 8). Therefore, stimulating the horizontal canal generates contralateral horizontal gaze. Conversely, a lesion of the horizontal canal results in ipsilateral gaze. Therefore, a lesion of the horizontal canal results in a tonic gaze deviation toward the side of the lesion, followed by a corrective saccade away from the side of the lesion (ie, nystagmus beats away from the lesion). For example, a left-sided vestibular lesion reduces input from the left horizontal semicircular canal, resulting in a leftward tonic gaze deviation, followed by a corrective saccade away from the side of the lesion. Thus, a left-sided lesion would produce leftward slow phases and right jerk nystagmus.

The anterior semicircular canals generate upgaze, and the posterior semicircular canals generate downgaze. Therefore, a unilateral vestibular lesion that affects the anterior and posterior canals on one side has no net effect on vertical gaze. However, the anterior and posterior canals generate contralateral torsion. Therefore, a unilateral vestibular lesion causes tonic ipsilateral torsion, followed by a corrective torsional saccade away from the side of the lesion.

Combining the effects of decreased afferent input from all 3 semicircular canals on 1 side, a unilateral peripheral vestibular lesion generates a combined horizontal–torsional nystagmus with jerk phases directed away from the side of the lesion. The nystagmus follows Alexander's law, which states that the nystagmus is more pronounced when gaze is directed toward the side of the fast-beating component. Depending on the severity of the lesion, the nystagmus may be evident in primary position. Asymmetric otolithic input may result in a skew deviation or an ocular tilt reaction (see Chapter 8).

A characteristic feature of peripheral vestibular nystagmus is the ability of visual fixation to damp the nystagmus. The clinician can evaluate the effect of visual fixation on nystagmus during direct ophthalmoscopy by temporarily covering the contralateral fixating eye. Other methods for enhancing vestibular nystagmus include vigorous head shaking, hyperventilation, mastoid vibration, and the Valsalva maneuver.

Peripheral vestibular dysfunction, often accompanied by nystagmus, usually occurs in 1 of 4 clinical patterns:

1. Acute monophasic disorder secondary to a (presumed viral) vestibular neuronitis.
2. Recurrent vestibular dysfunction, usually associated with auditory symptoms (eg, tinnitus and hearing loss). This disorder, exemplified by *Ménière disease*, is usually progressive, although there may be long symptom-free intervals.
3. Paroxysmal dysfunction of the vestibular system that produces vertigo in response to certain postures of the head. This disorder, known as *benign paroxysmal positional vertigo (BPPV)*, develops because of free movement of otoconia particles (calcium carbonate crystals normally contained within the utricle and saccule), which act as foreign debris within a semicircular canal. The Dix-Hallpike maneuver, during which the patient's head is turned 45° to the right or left and lowered

below the horizontal plane of an examining table to induce symptoms, can be used to determine on which side the semicircular canals are dysfunctional. Once the side is identified, repositioning treatments such as the Epley maneuver can remove the otoconia from that semicircular canal and provide lasting remission, although recurrence is not unusual.

4. Toxic vestibular dysfunction, primarily caused by the use of aminoglycosides (but also other medications such as chemotherapeutics). Systemic ototoxins typically produce head movement–related oscillopsia and decreased vestibular ocular reflex (VOR) gain bilaterally with little or no nystagmus (ie, vestibular hypofunction without asymmetry).

A very large cerebellopontine angle tumor (eg, vestibular schwannoma or meningioma) may produce *Bruns nystagmus*, which is a combination of gaze-evoked and peripheral vestibular nystagmus. Initially, because the vestibular nerve is affected, the eyes drift toward the side of the lesion, with a corrective fast phase in the opposite direction. As the lesion enlarges, the ipsilateral brainstem is compressed, causing problems in maintaining ipsilateral eccentric gaze; thus, as the patient looks to the side of the lesion, a large-amplitude, low-frequency, ipsilesional gaze-evoked nystagmus is noted, whereas in contralateral gaze (away from the side of the lesion), a small-amplitude, high-frequency, contralesional vestibular nystagmus is observed.

Baloh RW. Clinical practice. Vestibular neuritis. *N Engl J Med*. 2003;348(11):1027–1032.
Fife TD, Tusa RJ, Furman JM, et al. Assessment: vestibular testing techniques in adults and children: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(10):1431–1441.

Central Forms of Vestibular Nystagmus

Because the central vestibular structures of the brainstem and the cerebellum are extensively interconnected, it can be difficult, if not impossible, to determine the precise location of lesions that produce central nystagmus by clinical examination alone. Although some supranuclear ocular motility disorders provide localizing information (Table 9-2), it is often more useful to think of the central vestibular pathways as a single system and to obtain neuroimaging if more specific information about localization is desired. Central

Table 9-2 Selected Forms of Nystagmus or Oscillatory Movements and Their Most Common Lesion Locations

Abnormal Eye Movement	Probable Location of Lesion
Downbeat nystagmus	Cervicomedullary junction
Upbeat nystagmus	Posterior fossa (medulla most common)
Periodic alternating nystagmus	Cerebellar nodulus
See-saw nystagmus	Parasellar region/diencephalon
Ocular flutter/opsoclonus	Pons (pause cells), cerebellum (connections to pons)
Convergence-retraction nystagmus	Pretectum (dorsal midbrain)

vestibular nystagmus often involves pathways governed by the anterior semicircular canals, posterior semicircular canals, or both. Therefore, isolated vertical or torsional nystagmus is common (in contrast to peripheral vestibular nystagmus, which is characterized by horizontal movements combined with torsional movements). If central vestibular nystagmus is of small amplitude and present only outside primary position, patients may have no visual symptoms.

Downbeat nystagmus

Downbeat nystagmus is the most common form of central vestibular nystagmus and results from lesions that produce defective vertical gaze holding characterized by an upward drift of the eyes, which is then corrected with a downward saccade. Lesions that cause downbeat nystagmus compromise the vestibulocerebellum (ie, the nodulus, uvula, flocculus, and paraflocculus) and diminish the tonic output from the posterior semicircular canals to the ocular motor neurons. Downbeat nystagmus may be present in primary position, but in accordance with Alexander's law, the downbeating movements are usually accentuated in downgaze (especially to either side). Patients usually report oscillopsia, which can be debilitating.

A structural lesion may be associated with downbeat nystagmus, in which case the lesion is often located at the cervicomedullary junction. The most common structural lesion is an Arnold-Chiari type I malformation, a developmental abnormality characterized by posterior fossa crowding and cerebellar tonsillar protrusion into the foramen magnum (Fig 9-3). Lesions at the foramen magnum are best assessed with sagittal magnetic resonance imaging (MRI). In some cases of unexplained downbeat nystagmus, antibodies to glutamic acid decarboxylase (GAD) have been identified in the blood of affected patients. These antibodies might produce downbeat nystagmus by interfering with the γ -aminobutyric acid (GABA)-ergic neurons of the vestibular complex that normally inhibit the cells of the flocculus.

The differential diagnosis of downbeat nystagmus includes the following:

- Arnold-Chiari type I malformation
- syrinx of the brainstem or upper cervical spinal cord
- platybasia
- tumors of the foramen magnum (eg, meningioma, cerebellar hemangioma)
- demyelination
- stroke
- cranial trauma
- basilar artery impression
- spinocerebellar degenerations
- brainstem encephalitis
- paraneoplastic syndrome
- GAD antibodies
- drug toxicity (eg, lithium, anticonvulsants)
- impaired nutrition (ie, Wernicke encephalopathy, parenteral feeding, or magnesium deficiency)
- idiopathic

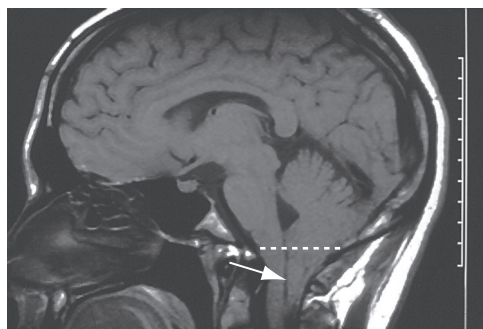


Figure 9-3 An Arnold-Chiari type I malformation in a 26-year-old patient who reported a sense of movement of his environment. Downbeat nystagmus was identified as the explanation for his oscillopsia. This T1-weighted sagittal magnetic resonance imaging (MRI) scan shows herniation of the cerebellar tonsils (*arrow*) through the foramen magnum. The level of the foramen magnum is shown by the *dotted line*.

Common off-label treatments (treatments prescribed for an indication other than those that have received approval from the US Food and Drug Administration) for downbeat nystagmus and other central vestibular forms of nystagmus include clonazepam (a GABA receptor agonist), baclofen, gabapentin, memantine, 4-aminopyridine, and 3,4-diaminopyridine (amifampridine). Unfortunately, medical treatment often provides little to no improvement of symptoms. Dalfampridine has been used to treat downbeat nystagmus and may be more efficacious than the similar drug 3,4-diaminopyridine. Base-out prisms (used to induce convergence) can sometimes improve the oscillopsia associated with downbeat nystagmus.

Upbeat nystagmus

Upbeat nystagmus is characterized by a downward drifting of the eyes, followed by corrective, upward saccades. Upbeat nystagmus may be caused by lesions in the brainstem (often medulla) or the anterior cerebellar vermis; thus, the lesions may exist at various locations within the posterior fossa. Common causes of upbeat nystagmus include demyelination, stroke, cerebellar degeneration, and tobacco smoking.

Torsional nystagmus

Although peripheral vestibular nystagmus may have a torsional component, purely torsional nystagmus indicates a central lesion. *Torsional nystagmus* is usually associated with a medullary lesion (eg, syringobulbia, lateral medullary infarction) and may be part of an ocular tilt reaction (see Chapter 8).

Periodic alternating nystagmus

Periodic alternating nystagmus (PAN) is a strictly horizontal nystagmus that oscillates predictably in direction, amplitude, and frequency. For instance, a rightward-beating nystagmus develops progressively larger amplitudes and higher frequencies up to a certain point, then wanes, eventually leading to a short period of downbeat or no nystagmus. Then the nystagmus reverses direction, with a crescendo–decrescendo pattern that again leads to a short period without nystagmus, completing the cycle. PAN may be congenital or acquired. The acquired form has a characteristic oscillation cycle of 2–4 minutes. A cursory examination may lead to the erroneous conclusion that the nystagmus is directed toward one side only. For this reason, any presentation of nystagmus that is purely horizontal and occurs in primary position should be observed for at least 2 minutes to be certain that the condition is not PAN. A patient with PAN may also demonstrate a periodic

alternating head turn (in the direction of the nystagmus) to minimize the nystagmus, in accordance with Alexander's law.

Acquired PAN is caused by unstable "velocity storage," typically secondary to vestibulocerebellar disease. As discussed in Chapter 8, the vestibular-ocular system's response to sustained head rotation attenuates fairly quickly as the cilia on the hair cells resume their normal position. However, a velocity storage mechanism prolongs the vestibular-ocular response for several seconds during sustained head movements. This velocity storage mechanism is generated by interconnections within the vestibular nuclei (the vestibular commissure) and is stabilized by cerebellar GABA-ergic innervation. Cerebellar disease may cause unstable velocity storage that results in a horizontal nystagmus with an oscillating null point, namely PAN. Common causes include Arnold-Chiari type I malformation, cerebellar degeneration, multiple sclerosis (MS), cerebellar tumors, stroke, use of anticonvulsant medication, and bilateral loss of vision. If the bilateral vision loss is reversed (eg, if a vitreous hemorrhage is cleared), PAN may be abolished. Baclofen, a GABA receptor agonist, can abolish the acquired form of PAN.

Acquired Pendular Nystagmus

Acquired pendular nystagmus includes pendular, slow-phase eye movements in the horizontal, vertical, and torsional planes (often forming elliptical waveforms). In contrast, congenital pendular nystagmus usually manifests with only horizontal movements. Pendular nystagmus with both vertical and horizontal components produces oblique nystagmus (if the components are in phase) or circular or elliptical nystagmus (if the components are out of phase). The eye movements may be conjugate or disconjugate and are often dissociated.

The localizing value of acquired pendular nystagmus is poor. It is most commonly observed in patients with MS, who may exhibit asymmetric or monocular forms. This form of nystagmus can also develop after blindness occurs secondary to optic nerve disease, including optic neuropathy due to MS. When vision is reduced in both eyes, the nystagmus is typically larger in the eye with poorer vision.

Memantine or gabapentin may reduce the severity of nystagmus and improve vision in patients with acquired pendular nystagmus. Unilateral retrobulbar injection of botulinum toxin type A reduces the amplitude of nystagmus and may improve vision for patients who are willing to view monocularly. However, total cessation of eye movements has its own consequences; for example, some patients report blurred vision when walking because of the loss of the normal VOR that adjusts eye position as the head moves.

Shery T, Proudlock FA, Sarvananthan N, McLean RJ, Gottlob I. The effects of gabapentin and memantine in acquired and congenital nystagmus: a retrospective study. *Br J Ophthalmol*. 2006;90(7):839–843.

Thurtell MJ. Treatment of nystagmus. *Semin Neurol*. 2015;35(5):522–526.

Oculopalatal Myoclonus or Tremor

Acquired pendular nystagmus may accompany *palatal myoclonus*, an acquired oscillation of the palate. The eye movements are continuous and rhythmic, occur at a frequency of

approximately 1 Hz, typically conjugate in the vertical plane, and persist during sleep. This eye movement disorder may also be associated with synchronous movements of the facial muscles, pharynx, tongue, larynx, diaphragm, trunk, and extremities. The condition usually arises several months (up to years in rare cases) after a lesion occurs that involves the Guillain-Mollaret triangle—a region that encompasses pathways that travel between the red nucleus, the inferior olivary nucleus, and the contralateral cerebellar nuclei. Lesions of this pathway produce inferior olivary hypertrophy, which is visualized with MRI as a T2 hyperintensity within 1 or both inferior olives.

See-Saw Nystagmus

See-saw nystagmus is a form of disjunctive nystagmus in which 1 eye elevates and intorts while the other eye depresses and extorts, a movement reminiscent of that of a see-saw. The eye movements are typically pendular, slow in frequency, and similar in amplitude between eyes. See-saw nystagmus may be congenital or acquired and may be caused by lesions that affect the chiasm, midbrain, or both. Trauma and parasellar-diencephalic tumors, in particular craniopharyngioma, are frequent causes; hydrocephalus and congenital achiasma are rare causes. There may be associated vision loss, often a bitemporal hemianopia. See-saw nystagmus may also occur in patients with vision loss due to retinitis pigmentosa, albinism, or optic nerve hypoplasia. Asymmetric vision loss may influence the amplitude of the eye movements (ie, the amplitude may be larger in the eye with poorer vision).

Dissociated Nystagmus With Internuclear Ophthalmoplegia

Lesions of the medial longitudinal fasciculus (MLF) produce an *internuclear ophthalmoplegia* (INO) (see Chapter 7). Isolated slowing of adduction of the eye ipsilateral to an MLF lesion is the primary feature required to establish a diagnosis of INO. In addition, nystagmus of the abducting eye often occurs when gaze is directed to the side opposite the lesion. One explanation for this pattern of dissociated nystagmus is the development of increased neural pulsing in an attempt to overcome the adduction weakness. According to Hering's law, the increased neural signaling is also delivered to the contralateral yoke muscle, causing excessive saccadic movements in the contralateral lateral rectus muscle.

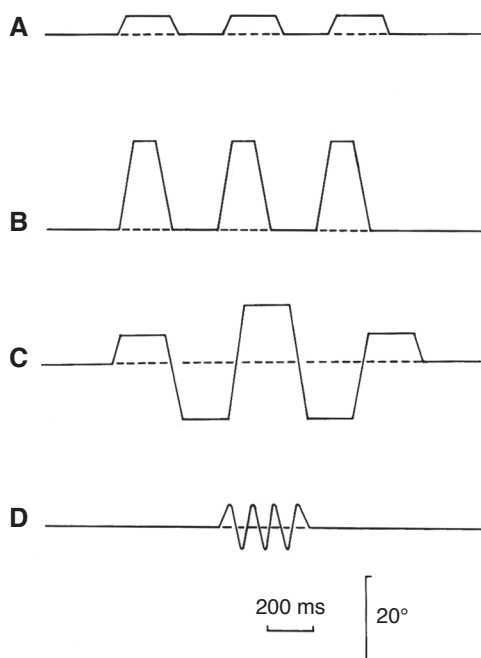
Saccadic Intrusions

Eye movement recordings have helped identify several forms of saccadic intrusions (Fig 9-4). Two classes of saccadic intrusions are distinguished by either the presence or the absence of an intersaccadic interval—the temporal separation between sequential saccades that lasts 180–200 milliseconds.

Saccadic Intrusions With Normal Intersaccadic Intervals

The most common saccadic intrusions are *square-wave jerks*, which have a normal intersaccadic interval (amplitude, typically $<2^\circ$; latency to refixation, 200 ms) and may occur

Figure 9-4 Schematic representation of saccadic intrusions and oscillations. The baseline of each graph represents on-target fixation. **A**, Square-wave jerks: small, intrusive saccades away from and back to the target position. **B**, Macrosquare-wave jerks. **C**, Macrosaccadic oscillations: hypermetric saccades to either side of the target position. **D**, Ocular flutter: back-to-back, to-and-fro saccades without an intersaccadic interval. (Modified with permission from Leigh RJ, Zee DS. *The Neurology of Eye Movements*. 3rd ed. Contemporary Neurology Series. New York: Oxford University Press; 1999.)



normally at low frequencies (4–6 per minute) in older patients. Pathologic square-wave jerks occur at a rate greater than 15 per minute. *Macrosquare-wave jerks* are much less common but also include an intersaccadic interval (amplitude, 5°–15°; latency to refixation, 70–150 ms). The larger-amplitude macrosquare-wave jerks tend to have a slightly higher frequency and are always pathologic. They are observed most frequently in patients with cerebellar disease or MS. Lesions of the cerebellum, brainstem, or their interconnecting fibers may alter the discharge of omnipause cells in the pons and burst cells in the paramedian pontine reticular formation (for horizontal saccades) (see Chapter 8). The inhibition of omnipause cells and the stimulation of burst cells lower the threshold for saccadic initiation, resulting in inappropriate saccadic intrusions that drive the eyes off of fixation.

Macrosaccadic oscillation is another saccadic intrusion that breaks fixation. Macrosaccadic oscillations differ from square-wave jerks in that they consist of large saccades that straddle and overshoot fixation without foveation of the target. The saccades are separated by an intersaccadic interval. The oscillations occur in bursts in which the saccadic amplitude increases and then decreases; eye movement recordings show a characteristic spindle shape. Macrosaccadic oscillations occur from cerebellar lesions (eg, tumors, MS, stroke, paraneoplastic syndromes) that alter the calibration of saccadic size, resulting in hypermetric primary and corrective saccades that oscillate around the desired eye position.

Saccadic Intrusions Without Normal Intersaccadic Intervals

Two types of eye movement abnormalities lack the intersaccadic interval that normally occurs between sequential saccades: (1) ocular flutter and (2) opsoclonus. *Ocular flutter* is characterized by bursts of involuntary, small-amplitude, very high-frequency (10–15 Hz) *horizontal* eye movements (see Fig 9-4D). *Opsoclonus* (also known as *saccadomania*),

however, consists of involuntary, *multidirectional* eye movements with a similarly high frequency but often larger amplitude. A patient may have ocular flutter and opsoclonus during the course of a disease. Both conditions can occur with myoclonus and ataxia (dancing eyes and feet syndrome). Ocular flutter and opsoclonus can be diagnosed with reasonable confidence through clinical examination, although a definitive demonstration of the lack of an intersaccadic interval requires eye movement recordings. The pathophysiology is unknown but may relate to cerebellar/brainstem dysfunction that inhibits omnipause neurons (located in the pons) and activates burst neurons (located in the paramedian pontine reticular formation and rostral interstitial nucleus of the medial longitudinal fasciculus), resulting in uncontrolled, involuntary horizontal and vertical saccadic intrusions (see Chapter 8).

Etiologies of ocular flutter and opsoclonus include paraneoplastic syndromes, encephalitis, drug intoxication, MS, environmental toxins, and hyperosmolar coma. Ocular flutter and opsoclonus may also occur in some patients without explanation in the absence of associated systemic abnormalities. Opsoclonus may be a transient finding that resolves by 6 months of age in otherwise-healthy infants.

Diagnostic workup for ocular flutter and opsoclonus includes searching for a tumor and an associated paraneoplastic syndrome. In children, neuroblastoma (or another tumor of neural crest origin) is the primary consideration, whereas in adults, small-cell carcinoma of the lung or cancer of the breast or ovaries is of prime concern. Evaluation consists of a complete physical examination and may include MRI or computed tomography (CT) of the head, chest, and abdomen; a whole-body positron emission tomography (PET) scan; lumbar puncture; and a test of urine catecholamine levels (to detect elevated homovanillic acid and vanillylmandelic acid, associated with neuroblastoma). Abnormal paraneoplastic antibodies may be found in the serum or cerebrospinal fluid of some patients with paraneoplastic syndrome-induced ocular flutter/opsoclonus. A serologic or cerebrospinal fluid assay for the immunoglobulin G anti-neuronal nuclear antibody type 2 (ANNA-2, or anti-Ri) can help confirm the diagnosis in cases that are secondary to cancer of the breast or ovary, whereas anti-neuronal nuclear antibody type 1 (ANNA-1, or anti-Hu) is present in some children with neuroblastoma. However, many patients with paraneoplastic syndromes do not have detectable anti-neuronal nuclear antibodies. Therefore, the absence of these antibodies does not exclude a paraneoplastic syndrome.

Treatment of ocular flutter and opsoclonus is directed at the underlying etiology. Regardless of etiology, immunomodulation with corticosteroids, plasmapheresis, intravenous immunoglobulin, or azathioprine may reduce the saccadic oscillations and associated oscillopsia. Other medications that may reduce symptoms include propranolol, verapamil, gabapentin, and thiamine.

Gordon LK. Paraneoplastic syndromes in neuro-ophthalmology. *J Neuroophthalmol*. 2015; 35(3):306–314.

Hoyt CS, Mousel DK, Weber AA. Transient supranuclear disturbances of gaze in healthy neonates. *Am J Ophthalmol*. 1980;89(5):708–713.

Voluntary Flutter (Voluntary “Nystagmus”)

Voluntary “nystagmus” consists of rapidly oscillating eye movements (almost always horizontal) that can be induced volitionally. These movements, which are not a form of

nystagmus (because they lack slow phases), appear as high-frequency, conjugate, back-to-back saccades without an intersaccadic interval. They are associated with convergence, facial grimacing, and eyelid fluttering. Episodes are unsustained, rarely lasting longer than 30 seconds. Voluntary nystagmus occurs in 8% of the normal population, may be familial, and is not associated with other neurological findings. At times, voluntary nystagmus can be difficult to distinguish from ocular flutter. Unlike voluntary nystagmus, ocular flutter may be sustained; is typically associated with other neurological signs (such as ocular dysmetria, ataxia, and myoclonus); and does not have the convergence, facial grimacing, and eyelid fluttering of voluntary nystagmus.

Additional Eye Movement Disorders

Convergence-Retraction Nystagmus

Convergence-retraction nystagmus does not meet the true definition of nystagmus because it lacks slow phases. This condition results from co-contraction of the extraocular muscles on attempted upgaze. The medial rectus muscles are the most powerful of the extraocular muscles, and their contraction produces convergent movements even when all other extraocular muscles are contracting. The co-contraction of all extraocular muscles causes retraction of the globe into the orbit. Convergence-retraction nystagmus localizes the disease process to the dorsal midbrain and is part of *dorsal midbrain syndrome* (see Chapter 8, Fig 8-5); therefore, this “nystagmus” is often associated with paresis of upgaze, pupillary light–near dissociation, skew deviation, and bilateral eyelid retraction (Collier sign). Convergence-retraction nystagmus is best demonstrated by having the patient attempt an upward saccade elicited on command or by following a downward-rotating OKN drum.

Superior Oblique Myokymia

Superior oblique myokymia (SOM) is characterized by monocular, paroxysmal, high-frequency bursts of superior oblique muscle contraction. These bursts typically last for seconds, occur numerous times per day, and produce vertical and torsional eye movements. The movements are of very small amplitude and usually require magnification (obtained, for instance, with a slit lamp or 20.00 D lens) to observe them. Using the slit lamp to focus on a conjunctival vessel can help identify these movements. The abnormal movements may occur either spontaneously or immediately after a downward eye movement or blinking. Patients may experience a combination of oscillopsia, vertical/torsional diplopia, blurry vision, and tremulous ocular sensations.

The etiology of SOM is unknown. Some clinical and neuroimaging findings suggest that this disorder may occur when the superior cerebellar or posterior cerebral artery compresses the cranial nerve (CN) IV root exit zone, similar to the neurovascular compression that occurs with hemifacial spasm and trigeminal neuralgia. In rare cases, SOM may occur prior to or after a CN IV palsy. Thus, CN IV compression, aberrant regeneration, and ephaptic transmission are implicated in the pathophysiology of this disorder.

Although most patients with SOM are otherwise healthy, in rare cases, SOM may be associated with MS, posterior fossa tumor, stroke, or trauma. Neuroimaging should be considered to identify any associated conditions.

The clinical course of SOM is variable. Some patients recover spontaneously or experience only brief spells of symptoms. Other patients experience chronic oscillopsia or intermittent diplopia. Treatment with β -blockers (topical or systemic), carbamazepine, phenytoin, baclofen, oxcarbazepine, or gabapentin may be helpful for some patients. A superior oblique tenectomy (to alleviate the oscillopsia) combined with an ipsilateral inferior oblique myectomy (to treat the iatrogenic superior oblique weakness) may help patients with more severe symptoms. In patients with neurovascular compression, intracranial surgery to decompress CN IV may alleviate symptoms. However, most patients choose a less invasive treatment option.

Agarwal S, Kushner BJ. Results of extraocular muscle surgery for superior oblique myokymia. *J AAPOS*. 2009;13(5):472–476.

Brazis PW, Miller NR, Henderer JD, Lee AG. The natural history and results of treatment of superior oblique myokymia. *Arch Ophthalmol*. 1994;112(8):1063–1067.

Hashimoto M, Ohtsuka K, Suzuki Y, Minamida Y, Houkin K. Superior oblique myokymia caused by vascular compression. *J Neuroophthalmol*. 2004;24(3):237–239.

Oculomasticatory Myorhythmia

Vertical saccadic palsy may be an early neurologic finding in Whipple disease. In addition, pendular vergence oscillations that occur with contractions of the masticatory muscles may develop. This combination of abnormal movements is known as *oculomasticatory myorhythmia*. Patients may have only the neurologic manifestations, but more commonly, they also have unexplained fever, diarrhea, cognitive dysfunction, weight loss, and lymphadenopathy. (A video of oculomasticatory myorhythmia is available at the NOVEL [Neuro-Ophthalmology Virtual Education Library] website at <http://novel.utah.edu>.) Whipple disease can be diagnosed through duodenal biopsy (using periodic acid–Schiff [PAS] staining) to document infection with *Tropheryma whipplei* or by serologic polymerase chain reaction (PCR) testing. Although Whipple disease is progressive and potentially life-threatening, it is curable with antibiotic therapy.

Schwartz MA, Selhorst JB, Ochs AL, et al. Oculomasticatory myorhythmia: a unique movement disorder occurring in Whipple's disease. *Ann Neurol*. 1986;20(6):677–683.

The Patient With Pupillary Abnormalities

Pupillary function is an important objective clinical sign in the assessment of patients with vision loss and neurologic disease. A relative afferent pupillary defect (RAPD) localizes the site of damage to the retina, optic nerve, optic chiasm, or optic tract. However, an RAPD does not produce anisocoria. Anisocoria may result from damage to or interruption of the innervation to the iris sphincter or dilator muscle or from external pharmacologic factors, reflecting asymmetric autonomic nerve input to each iris.

Pupillary anatomy and innervation are discussed in Chapter 1, and the evaluation of an RAPD is described in Chapter 3. This chapter reviews the clinical approach to patients with efferent pupillary disorders, including irregular pupils, anisocoria, and light–near dissociation.

History

Patients with pupillary disturbances, particularly anisocoria, might not be aware of any abnormality. This is especially true in individuals with dark-colored irides. Anisocoria is usually asymptomatic, but patients may report photophobia, difficulty focusing with changes in illumination, or blurring of vision. The clinician should inquire about any new medications, ocular infections, face or neck trauma, headache or facial pain, diplopia, or change in eyelid position. Examination of the patient should include an assessment of the orbit, eyelid position, and ocular motility.

Pupillary Examination

Examination of previous photographs (eg, a driver's license) may reveal whether the pupillary abnormality was present previously. Clinical examination of the pupils requires a bright, even, handheld light source (such as a muscle light); a pupil-measuring gauge, preferably in half-millimeter increments; and an examination room in which background illumination is easily controlled. Eye drops such as cocaine, hydroxyamphetamine, apraclonidine, or pilocarpine may also be used to help assess the pupils. To evaluate pupil size, the clinician shines a handheld light obliquely from below the nose for indirect illumination and a clear view of the pupils, in both darkness and room light. To avoid

accommodative miosis, the clinician asks the patient to fixate on a distant target and takes care not to block the patient's fixation.

To check the pupillary light reflex, the examiner briefly shines a bright focal light onto 1 pupil and notes the speed and amplitude of the pupil's constriction. Most clinicians observe only the illuminated pupil (the direct response) because it is difficult to simultaneously assess the consensual constriction of the contralateral pupil. In general, the direct and consensual pupillary responses are symmetric. Thus, shining a light onto a blind eye results in a poor pupillary response in both eyes, but if the light is moved onto the contralateral unaffected eye, both the pupil of the unaffected eye and the pupil of the blind eye (consensual response) constrict briskly. In other words, *poor vision in 1 eye is never a cause of anisocoria*.

If the light response is abnormal, the pupillary near response should be examined. This test should be carried out in moderate room light so that the patient's pupils are mid-sized. The clinician directs the patient to look at an accommodative target with fine detail. Although the near response is usually triggered by blurred or disparate imagery, it has a large volitional component, and the patient may need encouragement. Sometimes a better response is obtained if auditory input is added to the visual stimulus, such as a ticking watch, or if a proprioceptive target, such as the patient's own thumbnail, is used. A lack of near response usually indicates that the patient is not trying hard enough. Light–near dissociation should be diagnosed only when the near response exceeds the best constriction that bright light can produce.

Slit-lamp examination of the anterior segment is another essential part of the pupillary examination. Many ocular lesions can result in miosis, mydriasis, or poor pupillary response. Acute corneal injury or anterior chamber inflammation may explain a small pupil in the presence of ciliary spasm. In a patient with blurred vision, pain, red eye, and a dilated pupil, angle-closure glaucoma should be considered. Transillumination defects of the iris are evidence of iris damage from previous trauma, infection, or inflammation. Sectoral paralysis of the iris sphincter due to tonic pupil or aberrant regeneration of cranial nerve (CN) III is best observed by placing a wide beam at an angle to the iris and turning the light off and on while observing one sector of the sphincter at a time under high magnification. If the irides are intact, an innervational problem should be suspected.

Pharmacologic agents can be used to confirm a clinical suspicion of Horner syndrome, tonic pupil, or pharmacologic mydriasis. However, pharmacologic pupillary testing is not infallible; false-positive and false-negative test results can occur. Therefore, test results must be interpreted on an individual basis.

Baseline Pupil Size

Resting pupil size is influenced by several factors, including ambient light, state of retinal adaptation, level of arousal, and patient age. The frequency and amplitude of both pupils oscillate rhythmically and in synchrony; this phenomenon is called hippus. Hippus is independent of variations in illumination or in fixation of the eyes. Pupils typically become smaller as a result of aging. Sleepiness results in loss of cortical inputs that inhibit the Edinger-Westphal nucleus, thus causing small pupils. Severely elevated intraocular

pressure may result in enlargement of the pupil, possibly due to iris ischemia. Pupils are often dilated after generalized tonic-clonic seizures. Extremely small pupils suggest pontine hemorrhage, narcotic intoxication, or pilocarpine use. Extremely large pupils may be normal (especially in young patients) or may suggest parasympathetic pharmacologic blockade from use of topical or systemic drugs, use of stimulants, or a state of high anxiety.

Pupil Irregularity

Pupil irregularity can result from many factors that are either congenital or acquired. Congenital iris malformations such as coloboma or aniridia result in abnormal pupil shape and reactivity. Acquired conditions that damage the mechanical compliance of the iris stroma or iris musculature can result in an irregular pupil. Blunt trauma to the eye can cause focal tears in the sphincter muscle. An *iridodialysis* occurs when the outer edge of the iris is torn away from its ciliary attachment. Intraocular inflammation can damage the iris or cause it to adhere to the lens or cornea (*synechiae*). Neovascularization can also distort the iris and impair pupillary reactivity. A surgical procedure in the anterior segment may affect the shape or function of the pupil; cataract surgery is probably the leading cause of a misshapen pupil in an adult.

Two rare conditions of focal abnormality in iris innervation may cause pupillary irregularity:

1. *Tadpole pupil*. This disorder is attributed to a focal spasm of the iris dilator muscle, which produces a peaking of the pupil that lasts a few minutes. The phenomenon may occur numerous times over several days or a week and then disappear. It is idiopathic, but a small percentage of patients harbor an underlying sympathetic lesion; thus, pharmacologic testing for Horner syndrome is suggested.
2. *Midbrain corectopia*. In rare cases, eccentric or oval pupils are present in patients with rostral midbrain disease. The abnormality is presumably caused by incomplete damage of the pupillary fibers, leading to selective inhibition of iris sphincter tone.

Balaggan KS, Hugkulstone CE, Bremner FD. Episodic segmental iris dilator muscle spasm: the tadpole-shaped pupil. *Arch Ophthalmol*. 2003;121(5):744–745.

Anisocoria

Asymmetry of efferent signals to the iris muscles produces inequality in the diameters of the 2 pupils. This phenomenon, called *anisocoria*, may be physiologic or pathologic. Figure 10-1 shows an algorithm for evaluating a patient with isolated anisocoria. Specific disorders are discussed in the following sections.

Normal Pupillary Response to Light

When evaluating the pupils of a patient with anisocoria, the clinician should first check the pupillary light reflex (to determine whether the response to light is normal) and then evaluate whether the anisocoria is greater in dim or bright light. If the pupils react normally,

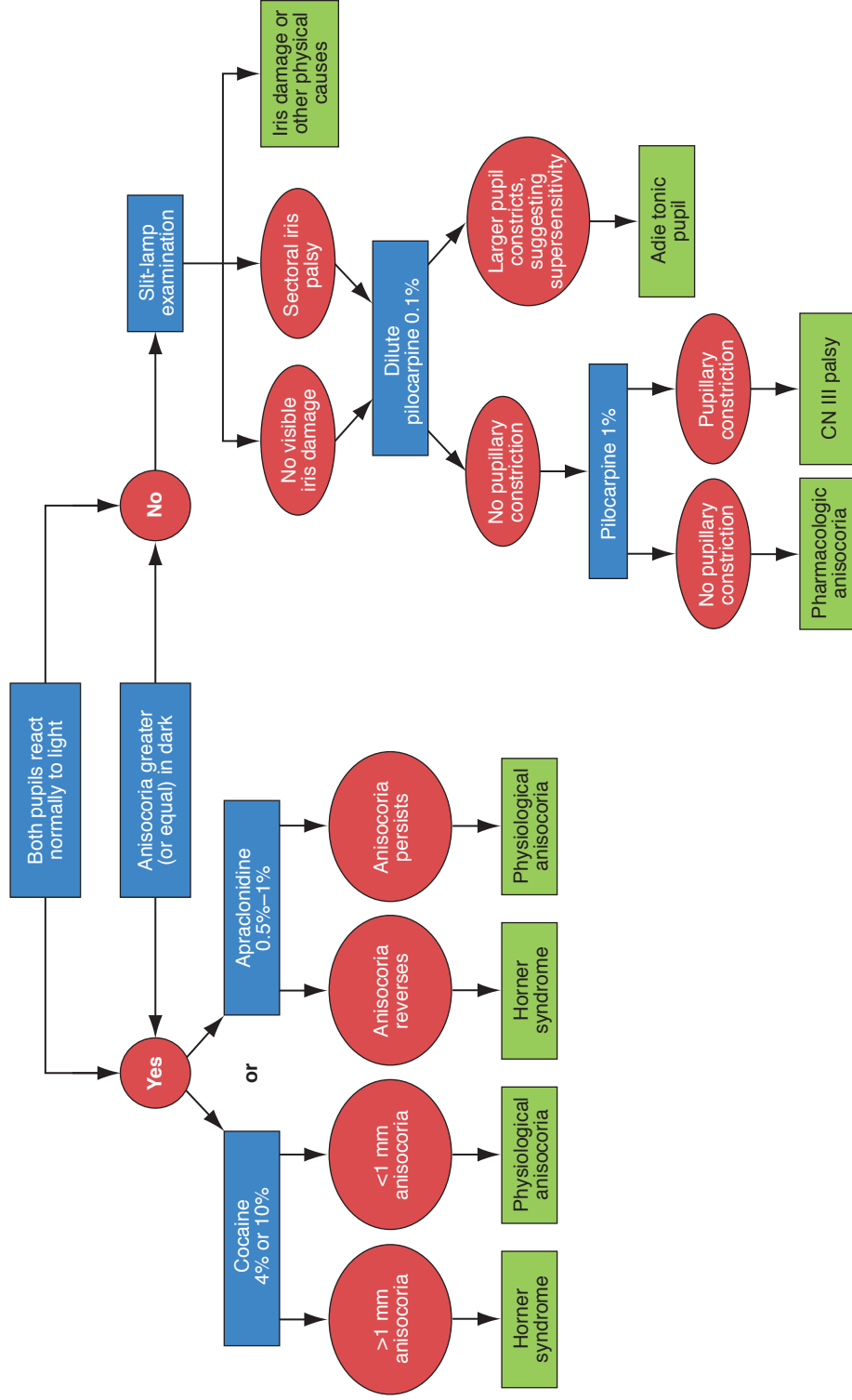


Figure 10-1 Flowchart for evaluation of anisocoria. CN = cranial nerve. (Based on an illustration by Helen Danesh-Meyer, MD.)

the abnormality is of the sympathetic pathway. If one of the pupils responds abnormally to light, the next step is to examine the iris sphincter at the slit lamp to determine whether there are any secondary causes that explain the anisocoria.

Anisocoria Equal in Dim and Bright Light

Physiologic anisocoria

When the magnitude of the anisocoria is equal in dim and bright light, this indicates that the relative function of the pupillary sphincter and dilator muscles is intact. This scenario is consistent with physiologic anisocoria, and the patient can be reassured about the benign nature of this phenomenon.

Physiologic anisocoria (also known as *simple* or *essential anisocoria*) is the most common cause of a difference in pupil diameter. About 20% of individuals have noticeably asymmetric pupils. Usually the difference in pupil diameter is less than 1.0 mm and can vary from day to day.

Sometimes physiologic anisocoria is more apparent in dim light than in bright light. Ptosis occurring on the side of the smaller pupil may create diagnostic confusion with Horner syndrome. Pseudo-Horner and true Horner syndromes are best differentiated through pharmacologic testing (see the section “Horner syndrome” in this chapter).

Lam BL, Thompson HS, Corbett JJ. The prevalence of simple anisocoria. *Am J Ophthalmol*. 1987;104(1):69–73.

Anisocoria Greater in Dim Light

Anisocoria that is greater in dim light may be caused by a range of conditions. Identifying some of the causes require obtaining a thorough patient history (eg, pharmacologic agents); others can be identified by slit-lamp examination (Table 10-1). In general, causes of anisocoria that have a mechanical or inflammatory origin tend to produce a sluggish pupillary response to light, unlike Horner syndrome and physiologic anisocoria.

Horner syndrome

The presence of a lesion at any point along the oculosympathetic pathway results in Horner syndrome, which is characterized clinically by ipsilateral miosis (from unantagonized action of the iris sphincter), facial anhidrosis, ipsilateral upper eyelid ptosis, and mild lower eyelid elevation (upside-down ptosis). The ptosis is due to denervation of the tarsal muscle (Müller muscle) in both the upper and the lower eyelids, producing a noticeably narrower palpebral fissure and the false impression of enophthalmos. In the acute phase, conjunctival hyperemia, facial flushing, and nasal congestion can also be present.

The distribution of anhidrosis depends on the location of the lesion. Interruption of the central (first-order) or preganglionic (second-order) neuron causes anhidrosis of the ipsilateral head, face, and neck. This may produce a harlequin syndrome, in which one-half of the face is pale and the other half is normal or reddish in color, with the division exactly in the midline. Interestingly, the pale side of the face is the one with the sympathetic deficit because the vessels and perspiratory glands have been denervated, leading to supersensitivity to circulating adrenaline.

Table 10-1 Causes of Anisocoria Greater in Dim Light and Sluggish Response to Light

Classification of Anisocoria	Examples of Causes
Pharmacologic anisocoria	Topical miotic: pilocarpine Systemic miotics: adrenergic blockers, general anesthesia, phenothiazines, narcotics, marijuana Parasympathomimetics: carbachol, methacholine, organophosphate, physostigmine Sympatholytics: α_1 -adrenergic antagonists, α_2 -adrenergic agonists (brimonidine)
Mechanical anisocoria	Posterior synechiae Trauma or surgery Anterior segment tumors Pseudoexfoliation (atrophy of iris dilator)
Inflammatory anisocoria	Anterior uveitis
Denervation anisocoria	Adie tonic pupil (long-standing Adie tonic pupil) Argyll Robertson pupil Aberrant regeneration of CN III

CN = cranial nerve.

Lesions at or distal to the superior cervical ganglion—that is, the postganglionic (third-order) neuron—result in anhidrosis limited to the ipsilateral forehead. When the lesion is congenital or acquired early in life, iris heterochromia develops (the affected iris appears lighter in color) but might not be detected until the age of 9–12 months.

One of the clinical challenges in diagnosing Horner syndrome is differentiating it from physiologic anisocoria, because the pupillary reaction to light is normal with both conditions, and physiologic anisocoria may also be greater in dim light. One key difference is that pupillary dilation is intact in physiologic anisocoria, whereas there is dilation lag in Horner syndrome. Pupillary dilation in dim light is the result of sphincter relaxation and dilator contraction. Hence, a normal pupil dilates briskly in dim light. When a sympathetic lesion is present, the affected pupil dilates only by sphincter relaxation. In Horner syndrome, the weakened dilator muscle causes the pupil to dilate more slowly, producing an anisocoria that is greatest at 4–5 seconds and less if remeasured at 15 seconds. The presence of dilation lag is sufficient to differentiate Horner syndrome from physiologic anisocoria.

The oculosympathetic dysfunction of the pupil can also be confirmed pharmacologically with topical eyedrops of either cocaine or apraclonidine. Cocaine blocks the reuptake of norepinephrine released at sympathetic nerve terminals in the eye, causing pupillary dilation, eyelid retraction, and conjunctival blanching in the unaffected eye. In Horner syndrome, little or no norepinephrine is released into the synaptic cleft. Therefore, cocaine has no effect, and the miotic pupil remains smaller than the fellow pupil. The test is performed by instilling 2 drops of cocaine, 4% or 10%, in each eye 5 minutes apart and measuring the degree of anisocoria after 45 minutes to 1 hour. A postcocaine anisocoria of 1 mm or greater is diagnostic of Horner syndrome on the side of the smaller pupil (see Fig 10-1). Eyes with iris synechiae and a mechanically immobile pupil can cause false-positive cocaine test results, but such findings can be readily distinguished through slit-lamp examination. In addition, after instillation of topical phenylephrine 10% (a strong,

direct-acting sympathomimetic drug), a mechanically restricted pupil will remain small, but in Horner syndrome, it will readily dilate.

Topical apraclonidine (0.5% or 1%), which is an α_2 -adrenergic agonist and a weak α_1 -adrenergic agonist, is used routinely as a pharmacologic diagnostic test for Horner syndrome (Fig 10-2). In most healthy eyes, apraclonidine has little effect on pupil size. In patients with Horner syndrome, the α_1 -agonist effect dominates because of the supersensitivity of the α_1 -receptors, resulting in relative mydriasis by contraction of the dilator muscle. For this test, 1 drop of apraclonidine is placed in each eye, and the patient is reassessed 60 minutes later (however, a positive result can often be detected before the 60 minutes have elapsed). Reversal of the anisocoria is considered a positive response and confirms the diagnosis of Horner syndrome. In addition to the pupillary dilation, the upper eyelid ptosis improves as well.

However, the role of apraclonidine has several limitations in the diagnosis of Horner syndrome. First, in theory, only postganglionic lesions should produce denervation supersensitivity. Although apraclonidine has been shown to trigger pupillary dilation in lesions at all levels of the sympathetic chain, the degree of sensitivity produced by central and preganglionic lesions is unclear. Second, denervation supersensitivity typically occurs several (2 to 5) days after injury to the sympathetic pathway; therefore, its role in acute lesions is questionable. In addition, apraclonidine is generally avoided in young children because it may cause central nervous system (CNS) depression or acute respiratory arrest. Cocaine remains a better choice for this age group, given its lower risk of adverse events. Brimonidine cannot be substituted for apraclonidine in pupil testing for Horner syndrome because it is a highly selective α_2 -adrenergic agonist and has no significant effect on the α_1 -receptor on the iris dilator.

Once a Horner syndrome is confirmed, it is possible to pharmacologically localize the lesion with topical hydroxyamphetamine (1%). Hydroxyamphetamine enhances the release of presynaptic norepinephrine from an intact postganglionic neuron; therefore, the pupil should dilate. If the pupil affected by Horner syndrome does not dilate, a lesion of the postganglionic neuron is suspected. If both pupils dilate well, the lesion is more proximal, in either the first- or second-order neuron (see Chapter 1, Fig 1-37). Because cocaine may interfere with the uptake and hence the efficacy of hydroxyamphetamine, 72 hours should elapse between the 2 tests.

Because commercial preparations of topical hydroxyamphetamine have been difficult to obtain and its use is associated with a high rate of false-negative results, hydroxyamphetamine for localization of Horner syndrome is rarely used in clinical practice. In

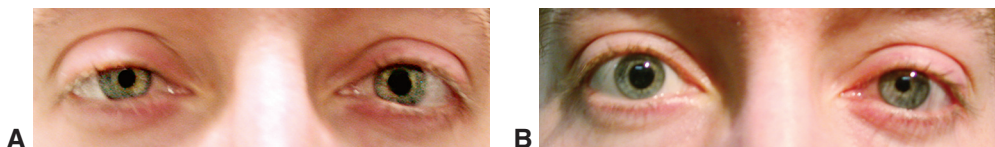


Figure 10-2 Apraclonidine test for Horner syndrome. **A**, A patient with suspected oculosympathetic defect (ptosis and miosis) on the right side. **B**, Following instillation of topical apraclonidine in both eyes, the right pupil has dilated and the anisocoria is now reversed, confirming Horner syndrome on the right side. Note also the resolution of eyelid ptosis, even to the point of retraction on the right side. (Courtesy of Aki Kawasaki, MD.)

most instances, the clinical presentation is sufficient to suggest the site of injury and the necessary evaluation (Table 10-2). The presence of neurologic signs such as ataxia, nystagmus, and hemisensory deficit suggests a medullary lesion, indicating a potential need for magnetic resonance imaging (MRI) of the brain and upper cervical cord. Symptoms such as arm pain, cough, hemoptysis, and swelling in the neck suggest a second-order (preganglionic) lesion in the superior sulcus (Pancoast syndrome) or in the mediastinum, necessitating cervicothoracic imaging (Fig 10-3). Symptoms associated with third-order (postganglionic) neuron injury include numbness over the first as well as the second or third divisions of CN V and double vision resulting from CN VI palsy, owing to the shared location of CN VI and oculosympathetic fibers in the cavernous sinus. Given the extent of the postganglionic fibers, modalities for investigation include MRI, with contrast, of the head, neck, and chest and magnetic resonance angiography (MRA) of the neck or computed tomography (CT) of the head, neck, and chest and computed tomography angiography (CTA) of the neck. If examination of old photographs confirms that Horner syndrome has been present for several years, further investigation will probably be unproductive.

Table 10-2 Features Associated With Horner Syndrome, Based on Lesion Location

Location or Etiology of Lesion	Common Symptoms or Specific Features
Central (first order)	
Lateral medullary syndrome (Wallenberg syndrome)	Anhidrosis of ipsilateral face Ipsilateral impairment of pain and temperature sensation over the face, contralateral pain and temperature impairment over the trunk and limbs, limb ataxia, bulbar disturbance (eg, dysarthria, dysphagia)
Trochlear nucleus/fascicle in brainstem	Contralateral CN IV palsy
Pontine lesion	Ipsilateral CN VI palsy
Spinal cord lesion	Quadri- or paraparesis, sensory deficit, bladder or bowel difficulty, hyperreflexia (Horner syndrome may be an isolated finding with cervical spondylosis, brainstem syrinx)
Preganglionic (second order)	
Apical lung (Pancoast syndrome; C8–T1 nerve roots)	Anhidrosis of ipsilateral face Cough, hemoptysis, and swelling in the neck; ipsilateral shoulder pain; pain and paresthesia along medial arm, forearm, and fourth and fifth digits
Neck lesion	Arm pain, hand weakness, history of neck surgery or trauma
Rowland-Payne syndrome (C6 nerve roots)	Paralysis of the phrenic, vagus, and recurrent laryngeal nerves
Brachial plexus injury	Ipsilateral hypochromia (mostly caused by birth trauma)
Lesion of the internal jugular vein	Central venous catheterization
Postganglionic (third order)	
Carotid artery dissection	Acute pain in temple, orbit, throat, neck, or arm or behind ear
Cavernous sinus lesion	Ipsilateral CN VI palsy, trigeminal neuropathy
Superior cervical ganglion lesion	Anhidrosis of forehead
Trigeminal autonomic syndromes (eg, cluster headache)	Headache, periocular pain, rhinorrhea, conjunctival tearing and injection
Intraoral trauma or tumor	Ear pain, hearing loss, vertigo

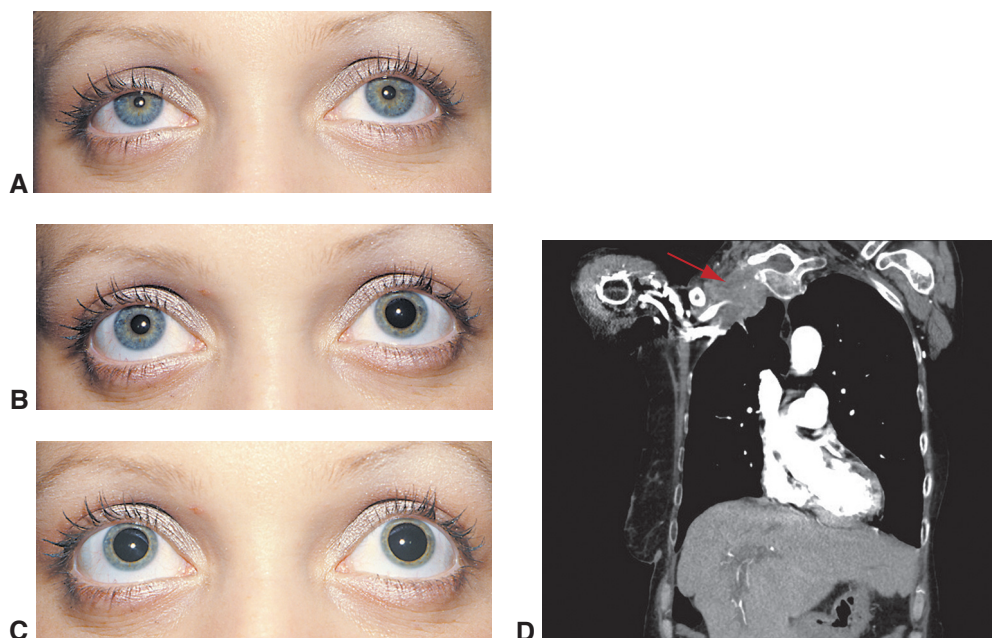


Figure 10-3 Horner syndrome involving the second-order neuron. **A**, This patient demonstrates right-sided ptosis and miosis in bright light. **B**, The anisocoria increases in the dark. **C**, Following instillation of hydroxyamphetamine eyedrops (1%), both pupils dilate, indicating that the third-order neuron is intact. **D**, CT scan demonstrates a right apical lung mass (Pancoast tumor) (arrow). (Parts A–C courtesy of Lanning B. Kline, MD; part D courtesy of M. Tariq Bhatti, MD.)

Horner syndrome associated with pain deserves special attention. Painful postganglionic Horner syndrome is a distinct clinical entity associated with several causes, most importantly an internal carotid artery dissection (Fig 10-4). Pain from dissection is usually located around the temple and orbit, and may extend to the throat. Patients with painful postganglionic Horner syndrome may also have amaurosis fugax and altered taste (dysgeusia). This condition must be recognized promptly because in the acute stage, stroke is a possible complication. MRI typically shows an intramural hemorrhage of the internal carotid artery, but in some cases, MRA, CTA, or, in rare instances, cerebral arteriography is needed to detect evidence of the dissection (see Chapter 14).

Trigeminal autonomic cephalgias, such as cluster headache, may also cause painful Horner syndrome during an acute attack (see Chapter 12). The Horner syndrome often resolves but may become permanent after repeated attacks. Some patients, usually middle-aged men, have Horner syndrome and daily unilateral headaches not characteristic of cluster headache. This condition, for which no underlying pathology can be identified, is called *Raeder paratrigeminal syndrome*. This syndrome is a diagnosis of exclusion made after careful evaluation for underlying pathology in the parasellar and cavernous sinus regions. If the site of the lesion is unknown, imaging of the brain, neck, spine, carotid arteries, chest, and pulmonary apex is indicated. This could be done with either MRI and MRA or CT and CTA.

Congenital Horner syndrome is usually caused by birth trauma to the brachial plexus. Nontraumatic Horner syndrome in infants and children raises the possibility of neuroblastoma arising in the sympathetic chain of the chest. In these circumstances, MRI of the

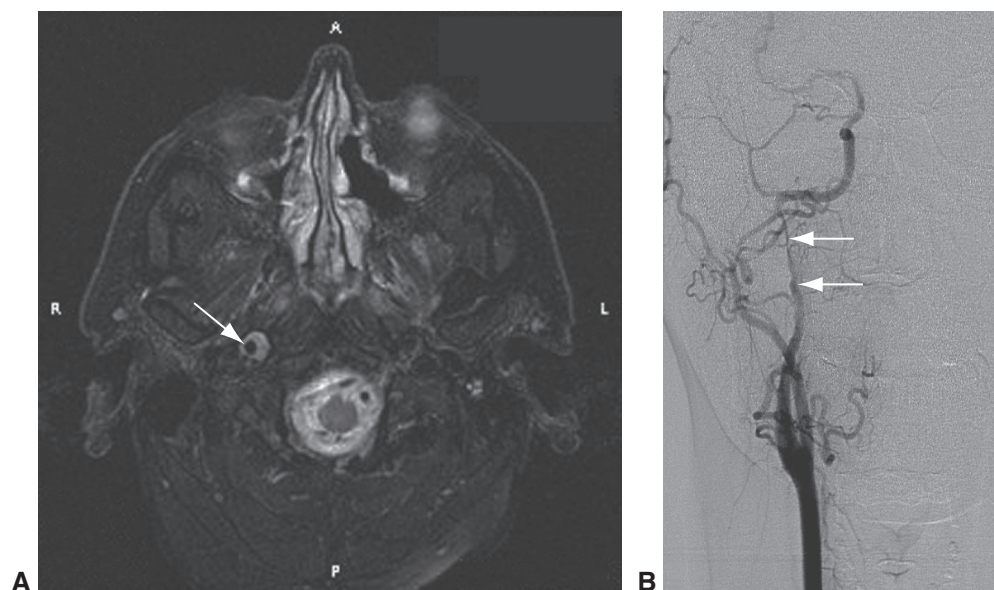


Figure 10-4 Internal carotid artery dissection. **A**, Axial magnetic resonance imaging (MRI) scan shows blood (arrow) in the wall of the right internal carotid artery ("crescent moon" sign). **B**, Catheter angiogram demonstrates "string" sign (arrows), confirming internal carotid artery dissection. A = anterior, L = left, P = posterior, R = right. (Part A courtesy of Karl C. Golnik, MD; part B courtesy of Lanning B. Kline, MD.)

head, neck, and chest is indicated. MRI of the abdomen may also be considered if clinical suspicion is high. Urinalysis for elevated levels of catecholamines and their metabolites is generally less sensitive than imaging studies in detecting neuroblastoma.

Barrea C, Vigouroux T, Karam J, Milet A, Vaessen S, Misson JP. Horner syndrome in children: a clinical condition with serious underlying disease. *Neuropediatrics*. 2016; 47(4):268–272.

Dewan MA, Harrison AR, Lee MS. False-negative apraclonidine testing in acute Horner syndrome. *Can J Ophthalmol*. 2009;44(1):109–110.

Mahoney NR, Liu GT, Menacker SJ, Wilson MC, Hogarty MD, Maris JM. Pediatric Horner syndrome: etiologies and roles of imaging and urine studies to detect neuroblastoma and other responsible mass lesions. *Am J Ophthalmol*. 2006;142(4):651–659.

Morales J, Brown SM, Abdul-Rahim AS, Crosson CE. Ocular effects of apraclonidine in Horner syndrome. *Arch Ophthalmol*. 2000;118(7):951–954.

Anisocoria Greater in Bright Light

Iris damage

Blunt trauma to the eye can cause miosis or mydriasis. The pupil may be relatively miotic after injury due to spasm, thereafter becoming midsized or mydriatic, with poor responses to light and near stimulation. Notches in the pupillary margin or transillumination defects near the sphincter muscle are evidence of sphincter damage. Mydriasis resulting from direct iris sphincter damage does not respond to topical pilocarpine (1% or 2%) and thus

mimics pharmacologic mydriasis. Slit-lamp examination should help the clinician differentiate traumatic mydriasis from other types of mydriasis. When iris injury occurs in patients with head trauma, the dilated pupil may be mistakenly identified as a sign of CN III palsy due to uncal herniation.

Prolonged or recurrent angle closure can also impair pupillary function, as can intra-ocular surgery (Urrets-Zavalía syndrome).

Pharmacologic mydriasis

When anticholinergic medications are accidentally or intentionally instilled in the eye, the pupil becomes dilated, and its reactivity to light and near stimulation is lost and accommodation is impaired. Drug-induced dilation causes paralysis of the entire sphincter, in contrast to a tonic pupil, which causes segmental sphincter paralysis. Slit-lamp examination can help the clinician make this distinction. When mydriasis is induced by an anticholinergic drug such as atropine, instillation of full-strength pilocarpine (1% or more) will not reverse the mydriasis. Mydriasis caused by neurologic disease such as Adie tonic pupil or CN III palsy is easily overcome with instillation of full-strength or even dilute pilocarpine. Pharmacologic mydriasis from topical dilating drops usually results in a large pupil, measuring greater than 7 mm. With adrenergic mydriasis, the pupil is large, the palpebral fissure is widened, and the conjunctiva may be blanched. Accommodation is not impaired. Pilocarpine 1% will cause some pupil contraction to an iris that has been dilated with α_1 -adrenergic agonists, but it won't be as much as in an eye without adrenergic mydriasis.

Adie tonic pupil

Damage to the ciliary ganglion or short ciliary nerves (postganglionic parasympathetic nerve injury) produces an Adie tonic pupil, which is characterized by a large pupil with poor reaction to light but a strong and tonic pupillary response to near vision (light–near dissociation). The pupil experiences a slow tonic redilation on looking from near to far distances. Other characteristics include sectoral palsy of the iris sphincter (Fig 10-5), accommodative paresis, and denervation cholinergic supersensitivity.

During the acute denervation phase of a tonic pupil, the pupil is dilated and poorly reactive to light stimulation and accommodative effort. Slit-lamp examination of the iris using high magnification can help the clinician distinguish functional sphincter segments

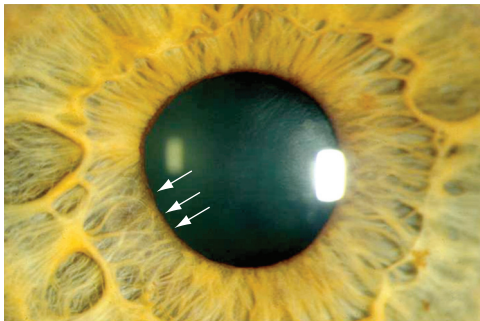


Figure 10-5 Sectoral palsy of the iris sphincter in Adie tonic pupil. The pupil is not round. The sphincter contraction is strongest along its superior sector, seen as a puckering or “bunching up” of the iris stroma. The sphincter is paralyzed between the 7-o’clock and 9-o’clock sectors (*arrows*); the adjacent area of iris stroma appears thinned out and flattened. (Courtesy of Rod Foroosan, MD.)

from nonfunctional sphincter segments. Iris crypts stream toward areas of normal sphincter function, and the stroma bunches up along the pupillary border in such areas, producing vermiform movements. Stromal thinning—even atrophy—is observed in areas of sphincter paralysis (see Fig 10-5).

As the damaged short ciliary nerves regenerate, misguided accommodative fibers sprout onto the iris sphincter, and the pupil recovers its ability to constrict in response to accommodative (or near) effort. However, pupillary movement (both constriction in response to an accommodative stimulus and subsequent redilation) is delayed and slow, that is, tonic (Fig 10-6). This effect may account for patient reports of difficulty refocusing when switching from near vision to distance. The pupillary light reflex typically remains severely impaired.

Idiopathic tonic pupil is known as Adie tonic pupil. Approximately 70% of patients are female. Tonic pupils are unilateral in 80% of cases, but the second pupil may become involved later (4% of unilateral cases per year). *Holmes-Adie syndrome* includes other features, notably, diminished deep tendon reflexes and orthostatic hypotension.

Pharmacologic testing can be used to confirm the diagnosis of Adie tonic pupil. The denervated iris sphincter is supersensitive to weak parasympathomimetic solutions, such as dilute pilocarpine eyedrops (0.1%). This pilocarpine strength can be obtained by diluting commercial 1% solution with balance salt solution, artificial tears, or sterile saline.

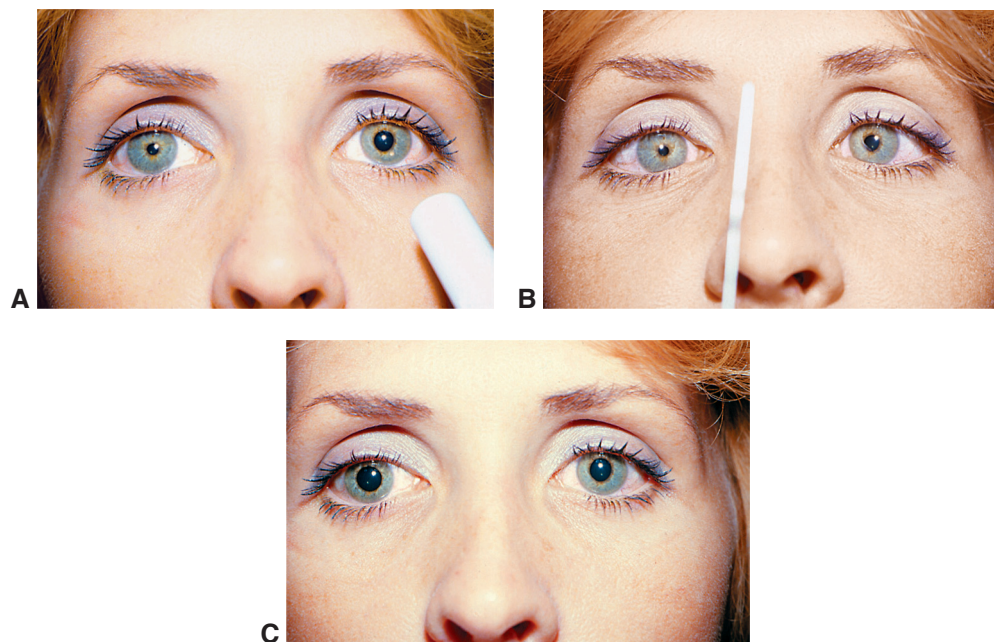


Figure 10-6 Left Adie tonic pupil. **A**, The left pupil reacts poorly to direct light stimulus, whereas the right pupil demonstrates a strong consensual response. **B**, Both pupils constrict as the patient fixates on a near target. The response of the left pupil to near effort is better than its response to light (light–near dissociation). **C**, After the patient refixates on a distant target, the right pupil quickly redilates. The left pupil is slow to redilate (it is smaller than the right pupil), a sign of tonicity. (Courtesy of Lanning B. Kline, MD.)

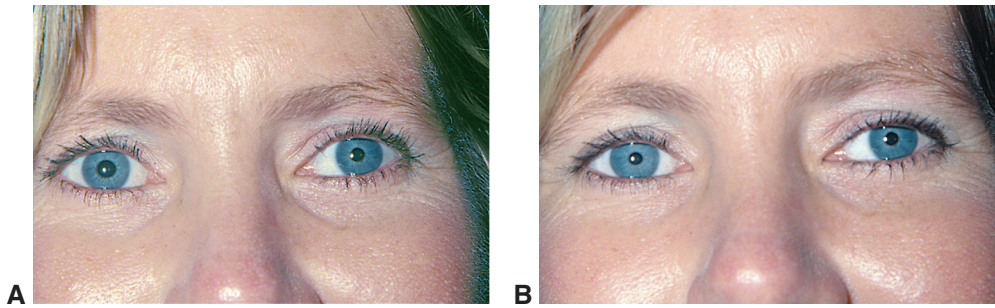


Figure 10-7 Right Adie tonic pupil and its response to pharmacologic testing **A**, Right Adie tonic pupil at baseline in ambient room lighting. **B**, After instillation of pilocarpine (0.1%), the right pupil becomes miotic, demonstrating supersensitivity. (Courtesy of Lanning B. Kline, MD.)

Sixty minutes after eyedrop application, the pupils are reexamined. If parasympathetic denervation is present, the affected pupil will have constricted more than the normal pupil (Fig 10-7). About 80% of patients with a tonic pupil demonstrate cholinergic supersensitivity, which develops within 5–7 days of denervation.

Patients with tonic pupils may have accommodative symptoms or photophobia but just as often are asymptomatic. Accommodative symptoms are difficult to treat but usually resolve spontaneously within a few months after onset. When photophobia is a problem, topical dilute pilocarpine (0.1%) may be helpful. With time (months to years), an Adie tonic pupil decreases in size but remains poorly reactive to light, resulting in anisocoria that is greater in the dark than in the light. Histologic examination of the ciliary ganglion in patients with Adie tonic pupil has shown a reduction in the number of ganglion cells.

A tonic pupil can be caused by local ocular or orbital processes such as surgery, trauma, laser procedure, infection (eg, herpes zoster virus, herpes simplex virus, syphilis, botulism), inflammation, or ischemia. Tonic pupils can also be a manifestation of widespread autonomic dysfunction consequent to diabetes mellitus, chronic alcoholism, dysautonomias, neurosyphilis, amyloidosis, sarcoidosis, the Miller Fisher variant of Guillain-Barré syndrome, or Charcot-Marie-Tooth disease. In addition to bilateral tonic pupils with mydriasis, botulism toxicity may also produce bilateral ptosis and ocular motility dysfunction.

Third cranial nerve palsy

Pupillary involvement in CN III palsy is almost always accompanied by ptosis and limited ocular motility (see Chapter 7). At times, the motility disturbance is subtle, requiring quantitation with prism and alternate cover testing. Pupillary dysfunction is an important factor in the evaluation of acute CN III palsy. When the pupil is involved, an aneurysm must be excluded (see Chapter 2, Fig 2-11). If the pupil is spared and all other functions of CN III are completely paretic, an aneurysm is unlikely, and microvascular ischemic disease is more probable.

Aberrant regeneration of CN III may cause mydriasis and a synkinetic pupillary reaction. (See images available at the NOVEL [Neuro-Ophthalmology Virtual Education

Library] website at <http://novel.utah.edu>.) Portions of the pupillary sphincter contract with attempted movement of the eye, especially medially.

Czarnecki JS, Thompson HS. The iris sphincter in aberrant regeneration of the third nerve.
Arch Ophthalmol. 1978;96(9):1606–1610.

Disorders of Pupillary Reactivity: Light–Near Dissociation

Light–near dissociation occurs when a near response exceeds the greatest pupillary constriction that bright light can produce. The physiologic basis for light–near dissociation is because the near reflex bypasses the pretectal nuclei in the dorsal midbrain and descends from higher cortical centers directly to the Edinger–Westphal nuclei. Light–near dissociation may arise from a variety of causes (Table 10-3).

Afferent Visual Pathway

Optic neuropathy is the most common cause of light–near dissociation (unilateral or bilateral). It is the result of damage to only the afferent limb of the pupillary light reflex (optic nerve); the central near impulses remain unaffected.

Midbrain

Dorsal midbrain damage can result in mid-sized pupils with poor light response and preserved near response. Such responses occur when the lesion spares the more ventrally

Table 10-3 Causes of Light–Near Pupil Dissociation

Cause	Location	Mechanism
Severe loss of afferent light input to both eyes	Anterior visual pathway (ie, retina, optic, nerves, chiasm)	Damage to the retina or optic nerve pathways
Panretinal photocoagulation, retinal cryotherapy, orbital surgery	Short posterior ciliary nerves	Aberrant regeneration of accommodative nerve fibers
Peripheral neuropathy	Short posterior ciliary nerves	Disproportionate loss of axons to iris sphincter
Adie tonic pupil	Ciliary ganglion	Aberrant regeneration of iris sphincter by accommodative neurons
Aberrant regeneration of CN III	CN III	Aberrant regeneration of iris sphincter by accommodative neurons or extraocular muscle neurons
Loss of pretectal light input to Edinger–Westphal nucleus	Midbrain tectum	Infection (eg, Argyll Robertson pupils secondary to syphilis) compression (eg, pinealoma), ischemia (eg, stroke)

CN = cranial nerve.

located fibers of the near reflex pathway. Associated findings include bilateral eyelid retraction (Collier sign), vertical gaze palsy, accommodative paresis, and convergence-retraction nystagmus (Parinaud syndrome; see Chapter 8, Fig 8-5).

Argyll Robertson pupil occurs in patients with tertiary syphilis involving the CNS. Affected patients have small pupils (<2 mm in diameter) that are often irregular. The pupils do not react to light, but the near response and subsequent redilation are normal and brisk. These characteristics distinguish Argyll Robertson pupils from bilateral chronic tonic pupils (which may also result from neurosyphilis). In addition, iris atrophy frequently occurs, portions of the iris transilluminate, and dilation is poor after instillation of mydriatic eyedrops.

Argyll Robertson–like pupils are observed in widespread autonomic neuropathies such as bilateral tonic pupils (chronic), diabetes mellitus, and chronic alcoholism, as well as in encephalitis and after panretinal photocoagulation. Serologic tests for syphilis should be considered in the evaluation of patients with bilateral pupillary light–near dissociation with miosis.

Aberrant Regeneration

Light–near dissociation can also result from aberrant regeneration of damaged nerves that restores the near reflex but not the light reflex. Misdirected growth can occur after traumatic injury or chronic compression of CN III. Sometimes aberrant regeneration involves the medial rectus fibers and pupillary contraction occurs during attempted adduction. This synkinetic pupil movement can resemble light–near dissociation.

Other Pupillary Disorders

Benign Episodic Unilateral Mydriasis

Also known as *springing pupil*, benign episodic unilateral mydriasis typically occurs in young, healthy individuals who frequently have a history of headache. Episodic mydriasis may last from minutes to hours and may be accompanied by mild blurring of vision, periocular discomfort, and headache. Each episode is self-limited, and the condition has not been associated with any systemic or neurologic disease.

Jacobson DM. Benign episodic unilateral mydriasis: clinical characteristics. *Ophthalmology*. 1995;102(11):1623–1627.

CHAPTER 11

The Patient With Eyelid or Facial Abnormalities



This chapter includes a related video, which can be accessed by scanning the QR code provided in the text or going to www.aao.org/bcscvideo_section05.

Eyelid abnormalities and facial movement disorders are frequently encountered in ophthalmology. Many such problems are neurologic in origin and therefore require careful evaluation. A thorough history of the presenting complaints is essential, as is documentation of concomitant medical conditions. Although most patients are aware of an abnormality in the position or function of the eyelid, some may present instead with a chief concern of visual difficulties (eg, visual loss from ptosis) or pain (eg, exposure keratopathy from facial palsy). Occasionally, patients will attribute the problem to the wrong eye, for example mistaking ptosis for contralateral eyelid retraction, or widening of the palpebral fissure for contralateral ptosis. The clinician should ask about onset and duration of symptoms, as well as associated symptoms. In addition, the clinician should perform a careful evaluation of eyelid function and facial movements along with a thorough ophthalmic examination. Diagnosis and management of eyelid disorders are discussed at greater length in BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*.

Examination Techniques

An examination of the eyelids begins by observing their general shape and appearance (eg, an S shape may indicate pathology affecting the lacrimal gland or neurofibromatosis [Fig 11-1; see also Chapter 14]) and blink rate (eg, low in Parkinson disease and high



Figure 11-1 Ptosis in a 2-year-old with neurofibromatosis; the S-shaped eyelid margin results from the presence of a plexiform neurofibroma. (Courtesy of Steven A. Newman, MD.)

in blepharospasm), and by noting abnormal movements (eg, synkinesis with other facial muscles). If the ptosis is unilateral, the clinician should verify that it is not an artifact of vertical strabismus (eg, hypotropia; Fig 11-2) or contralateral eyelid retraction. The eyelids should be everted for examination to rule out a local cause of ptosis, such as retained contact lens or giant papillary conjunctivitis. If the ptosis is asymmetric, the clinician should manually raise the ptotic eyelid to see if the higher eyelid drops to a new position (Fig 11-3).

When evaluating a patient with ptosis, the clinician should obtain the following 5 important clinical measurements:

1. levator palpebrae superioris muscle function
2. margin-reflex distance
3. vertical palpebral fissure height
4. upper eyelid crease position
5. lagophthalmos amount (if present)

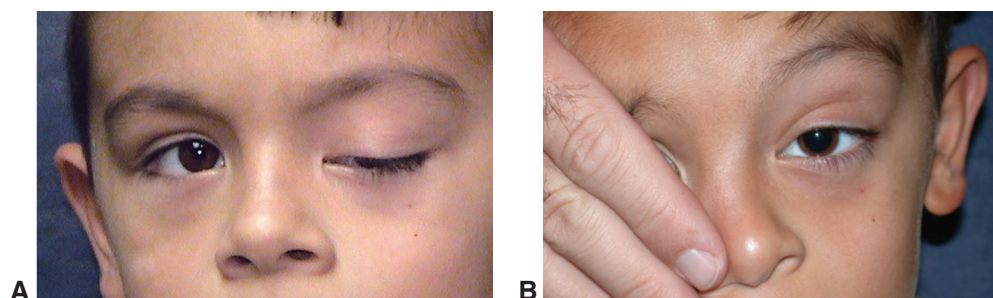


Figure 11-2 Pseudoptosis. **A**, Patient with pseudoptosis from a large left hypotropia. **B**, Occlusion of the right eye revealed markedly improved upper eyelid position. (Courtesy of M. Tariq Bhatti, MD.)

Figure 11-3 Myasthenia gravis. **A**, Patient with myasthenia gravis and ptosis that is greater on the left side than on the right. **B**, Manual opening of the left eyelid results in greater right-sided ptosis (enhanced ptosis). This sign, although often present with myasthenia gravis, is not specific. It may occur with other disorders producing asymmetric ptosis and is a manifestation of Hering's law of equal innervation. (Courtesy of Rod Foroozan, MD.)



Descriptions of these measurements are provided in Chapter 12 of BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*.

In addition, eyelid movement during target pursuit from upgaze to downgaze should be observed. Normally, such movement is smoothly accomplished, but lid lag may occur in patients with thyroid eye disease or as a result of aberrant regeneration of cranial nerve (CN) III (see Chapter 7, Fig 7-10).

To aid diagnoses of cases of suspected fatigable ptosis caused by myasthenia gravis, the patient can be asked to fixate on the clinician's hand, which is elevated to provoke extreme upgaze. The clinician watches for progressive ptosis as the patient attempts to hold this position. A patient without myasthenia gravis can maintain the position without developing ptosis. The Cogan lid-twitch sign, a feature of myasthenia gravis, can be identified by having the patient fixate in downgaze for a few seconds and then rapidly refixate straight ahead. The sign appears as an upward overshoot of the eyelid followed by fluttering as the eyelid settles into position (videos of lid twitch and lid twitch sign are available at The Neuro-Ophthalmology Virtual Education Library [NOVEL] website at <http://novel.utah.edu>).

Evaluation of facial motor function includes assessing the strength of the orbicularis oculi and other facial muscles. Eyelid closure should be assessed to determine if it is incomplete (lagophthalmos). Reinnervation phenomena, such as synkinesis with eyelid closure and facial tics, may be signs of a previous injury to CN VII (Fig 11-4). The clinician should note the presence of exophthalmos (eg, thyroid eye disease) or enophthalmos. Enophthalmos may result in apparent ptosis and narrowing of the palpebral fissure because the eyelid follows the contour of the globe as the eye retracts into the orbit. Anisocoria (see Chapter 10) may suggest sympathetic nervous system disruption, which will alter eyelid position. Dysfunction of CN III with parasympathetic nervous system involvement may also present with ptosis and anisocoria, as well as an ocular motility deficit. Finally, “neighboring” CNs should be assessed. If ptosis is caused by CN III weakness, the functions of CN IV, CN V, and CN VI should also be evaluated. Ocular motility should be



Figure 11-4 Facial nerve synkinesis. Misdirection may occur with recovery of CN VII function. **A**, In this 54-year-old patient, aberrant regeneration of left CN VII after resection of a cerebellopontine angle meningioma caused eyelid closure when she attempted to smile (**B**). (Courtesy of Steven A. Newman, MD.)

checked for subtle weakness. Similarly, if CN VII dysfunction is found, facial sensation and hearing should be evaluated.

Ptosis

Congenital Ptosis

The most common form of congenital ptosis is thought to result from dystrophic development of the levator palpebrae superioris muscle without associated innervational abnormalities. Congenital ptosis is typically associated with decreased levator function, lid lag on downgaze, and poorly formed (or absent) upper eyelid crease. Congenital ptosis (Fig 11-5) may be unilateral or bilateral and may be associated with other congenital ocular or orbital abnormalities, including blepharophimosis syndrome, congenital fibrosis of the extraocular muscles, superior rectus weakness or overaction, and Marcus Gunn jaw-winking syndrome (Fig 11-6). This last phenomenon is a synkinetic movement of the eyelid associated with jaw movement. In the external pterygoid–levator form of the syndrome, the eyelid elevates with movement of the mandible to the opposite side, jaw protrusion, or wide opening of the mouth. With the internal pterygoid–levator form, the eyelid elevates when the teeth are clenched. In some patients with Marcus Gunn jaw-winking syndrome, ptosis may worsen with movement of the jaw, although this finding is not common. Congenital tumors, such as hemangiomas and neurofibromas (see Fig 11-1) may also lead to congenital ptosis. Such tumors are typically associated with a palpable mass. Congenital CN III palsy and congenital Horner syndrome are relatively rare causes of congenital

Figure 11-5 Congenital ptosis of the right upper eyelid in a 2-year-old child. (Courtesy of Rod Foroozan, MD.)



Figure 11-6 Marcus Gunn jaw-winking syndrome. **A**, This 25-year-old has mild right upper eyelid ptosis. **B**, Opening the mouth results in eyelid retraction. This pattern indicates synkinesis between CN V and CN III. (Reprinted with permission from Levin LA, Arnold AC, eds. *Neuro-Ophthalmology: The Practical Guide*. New York: Thieme; 2005.)

neurogenic ptosis. Whatever the origin of a child's congenital ptosis, the ophthalmologist must be aware of the potential for amblyopia as a result of occlusion or anisometropia.

Acquired Ptosis

Table 11-1 lists the most common causes of acquired ptosis. *Neurogenic ptosis* requires careful attention to associated abnormalities in pupillary size and extraocular movements. Bilateral ptosis may be the only manifestation of a nuclear CN III palsy (see Chapter 7). *Cerebral ptosis*, which is a rare form of ptosis, occurs in association with a lesion of the cerebral (typically right) hemisphere. The ptosis may be bilateral or unilateral, and in the majority of cases, it is transient, lasting up to several months.

Suspicion of the presence of systemic disorders such as *myasthenia gravis*, *chronic progressive external ophthalmoplegia*, *oculopharyngeal dystrophy*, and *myotonic dystrophy* (discussed in Chapter 14) requires questions regarding the patient's general strength, fatigability, dysphagia, and family history. *Botulism* leads to bilateral ptosis associated with poorly reactive pupils and ophthalmoplegia. Such patients also have associated facial paralysis and generalized proximal muscle weakness. Areflexia, ataxia, and ophthalmoplegia characterize *Miller Fisher syndrome*, a variant of Guillain-Barré syndrome (discussed later in this chapter). In addition to bilateral ptosis, patients with Miller Fisher syndrome may also have facial diplegia, as well as respiratory and swallowing difficulties. Long-term use of steroid eyedrops is thought to lead to ptosis as a localized steroid-induced myopathy of the levator muscle. Posterior sub-Tenon steroid injections have also been associated with ptosis. The levator muscle, aponeurosis, or the insertion site of the aponeurosis may be adversely affected by such injections.

Levator aponeurotic defects have been found to be the most frequent cause of acquired ptosis, supplanting the idea that acquired ptosis is the result of aging ("senile" ptosis). This ptosis is caused by stretching, dehiscence, or disinsertion of the levator aponeurosis. Aponeurotic ptosis may occur with frequent eye rubbing or prolonged contact lens use, and may also be caused or exacerbated by intraocular surgery, perhaps resulting from use of an eyelid speculum. Because the levator muscle itself is healthy, levator function is usually normal. Patients with aponeurotic defects usually have a high eyelid crease.

Table 11-1 Causes of Acquired Ptosis

Aponeurotic	Neurogenic
Attenuation	Apraxia of eyelid opening
Disinsertion	CN III palsy
Mechanical	Horner syndrome
Chalazion	Miller Fisher syndrome
Cicatricial	Ophthalmoplegic migraine
Myogenic	Neuromuscular
Chronic progressive external ophthalmoplegia	Botulism or botulinum toxin
Long-term use of steroid eyedrops	Myasthenia gravis
Myotonic dystrophy	Traumatic
Oculopharyngeal muscular dystrophy	Eyelid laceration
	Foreign body
	Postsurgical ptosis

Traumatic and mechanical causes of acquired ptosis are generally evident from inspection of the eyelids and require appropriate medical or surgical therapy.

Pseudoptosis

Pseudoptosis encompasses conditions that mimic true ptosis, such as brow ptosis and laxity and dermatochalasis. Pseudoptosis can also be caused by microphthalmos or by phthisis bulbi, conditions resulting in the eyelids being inadequately supported by the globe. Hypotropia also causes pseudoptosis, because the perception of eyelid position is related to the position of the eye (see Fig 11-2). Contralateral eyelid retraction may also give rise to pseudoptosis.

Apraxia of Eyelid Opening

Apraxia of eyelid opening is a rare disorder that causes unilateral or bilateral ptosis (Video 11-1). Thought to be supranuclear in origin, it is characterized by the inability to open the eyelids voluntarily, related to frontalis contraction and facial grimacing. It is often associated with extrapyramidal disease such as Parkinson disease, multiple system atrophy, Huntington disease, Wilson disease, and progressive supranuclear palsy. The disorder has also occurred after bilateral frontal lobe infarcts. Apraxia of eyelid opening may also occur in patients with benign essential blepharospasm.



VIDEO 11-1 Apraxia of eyelid opening.

Courtesy of M. Tariq Bhatti, MD.

Access all Section 5 videos at www.aao.org/bcscvideo_section05.



Eyelid Retraction

Eyelid retraction is present if the sclera is visible above the superior corneal limbus when the eyes are in primary position. It is usually acquired but may be present at birth. Preterm infants occasionally have a benign transient conjugate downgaze associated with upper eyelid retraction. In many healthy infants (80% of children 14–18 weeks of age), bilateral eyelid retraction (eye-popping reflex) occurs when ambient lighting levels are reduced.

Table 11-2 lists the causes of acquired eyelid retraction. In adults, the most common cause is thyroid eye disease (Fig 11-7). The eyelid retraction (*Collier sign*) in *dorsal midbrain syndrome* (see Chapter 8, Fig 8-5) is a less common cause. Unilateral eyelid retraction can develop as a result of contralateral ptosis (pseudo-eyelid retraction); this phenomenon results from Hering's law of equal innervation. Bilateral eyelid retraction can be associated with thyroid eye disease, familial periodic paralysis, Cushing syndrome, and midbrain disease, or hydrocephalus with vertical nystagmus. Unilateral eyelid retraction is caused chiefly by thyroid eye disease but may also occur from aberrant regeneration of CN III (see Chapter 7), Marcus Gunn jaw-winking syndrome (see Fig 11-6), idiopathic levator fibrosis, carcinomatous infiltration, or iatrogenic causes (strabismus surgery on the vertical rectus muscles or ptosis repair). Several surgical procedures have been used to reduce the degree of eyelid retraction in patients with thyroid eye disease. See BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*, for a review of eyelid retraction treatment methods.

Table 11-2 Causes of Acquired Eyelid Retraction**Mechanical**

Buphthalmos
 High axial myopia
 Orbital fracture with entrapment
 Proptosis secondary to orbital mass

Myogenic

Carcinomatous infiltration
 Postsurgical (ptosis repair, orbicularis myectomy, strabismus surgery on vertical rectus muscle)
 Thyroid eye disease

Neurogenic

Aberrant regeneration of CN III
 Dorsal midbrain syndrome
 Long-term use of sympathomimetic eye drops (eg, phenylephrine, apraclonidine)
 Marcus Gunn jaw-winking syndrome
 Progressive supranuclear palsy

Pseudo-eyelid retraction (secondary to contralateral ptosis)

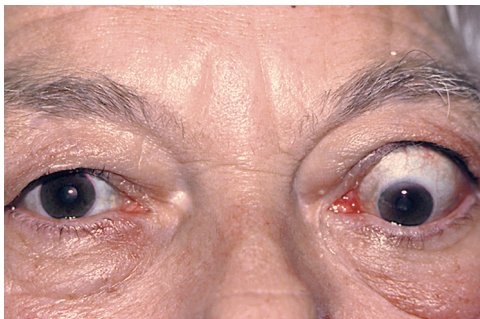


Figure 11-7 Eyelid retraction from thyroid eye disease. This 73-year-old woman presented with a 6-month history of foreign-body sensation (previously treated as “dry eye syndrome”). Eyelid retraction on the left side is enhanced by severe left inferior rectus restriction. (Courtesy of Steven A. Newman, MD.)

Abnormalities of Facial Movement

The ophthalmologist may be asked to evaluate CN VII weakness, which is frequently seen in clinical settings. Assessment of CN VII includes testing not only motor function, but also sensory and autonomic functions. Motor function can be readily assessed by observation. With the patient at rest, any asymmetry of facial expression or eyelid blink is noted. The palpebral fissure on the side of CN VII paresis will be wider as a result of the relaxed tone of the orbicularis oculi muscles. The clinician can test the various muscle groups by asking the patient to smile, to close the eyes forcibly, and to wrinkle the forehead. The degree to which the eyelashes become buried on each side can reveal subtle orbicularis oculi weakness. The corneal blink reflex provides a functional assessment of CN VII and CN V.

Testing autonomic functions such as salivation and lacrimation as well as testing sensation can help localize CN VII lesions. Cutaneous sensation can be tested along the posterior aspect of the external auditory canal. Lesions of CN VII from the cerebellopontine angle to the geniculate ganglion typically impair all functions of the nerve, whereas lesions distal to the geniculate ganglion affect only certain functions, depending on their location (Fig 11-8).

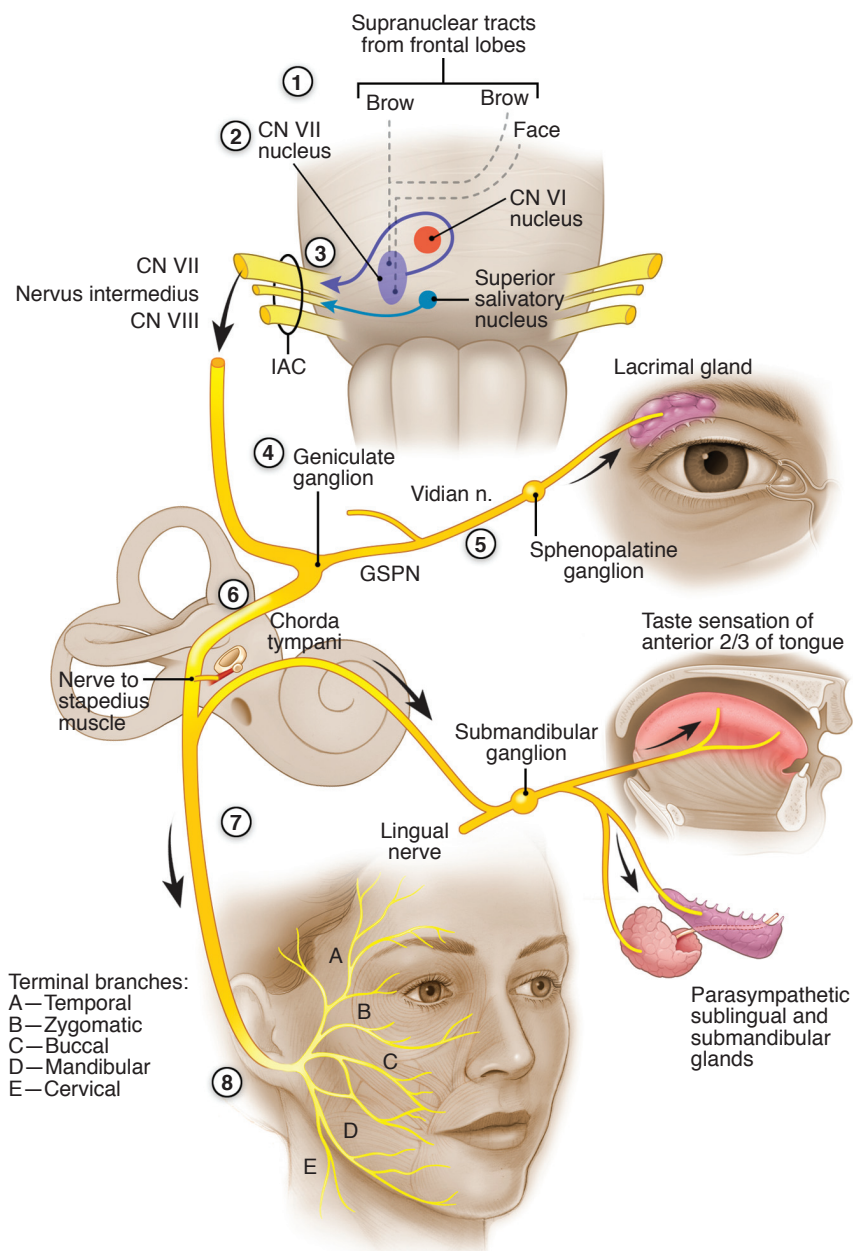


Figure 11-8 Distribution and topical diagnosis of CN VII lesions.

1. *Supranuclear facial palsy*: contralateral weakness of lower two-thirds of the face with accompanying weakness of the orbicularis oculi muscle; retained expression
2. *Nuclear facial palsy*: facial monoplegia (congenital) plus CN VI nucleus involvement (ipsilateral gaze palsy) and frequent ataxia; occasional Horner syndrome

(Continued)

Figure 11-8 (continued) Peripheral lesions result in facial monoplegia, including the orbicularis oculi and frontalis muscles, as well as:

3. *Cerebellopontine angle*: decreased tearing, dysgeusia, loss of salivary secretion, loss of taste from anterior two-thirds of tongue, hearing impairment, nystagmus, vertigo, ataxia, and adjacent CN findings (CN V, CN VI)
4. *Geniculate ganglionitis* (Ramsay Hunt syndrome, herpes zoster oticus): findings are the same as in cerebellopontine angle, but the brainstem and other CNs are not involved
5. *Isolated ipsilateral tear deficiency* due to involvement of vidian nerve or sphenopalatine ganglion (accompanying CN VI palsy with cavernous sinus involvement)
6. *Fallopian canal*: involvement of nerve to stapedius muscle, dysacusis, involvement of chorda tympani, loss of taste to anterior two-thirds of tongue, impaired salivary secretion
7. *Distal to chorda tympani*: isolated paralysis of facial muscles
8. *Distal to branching of CN VII after it leaves stylomastoid foramen*: only certain branches of CN VII are affected (localized facial; bilateral CN VII palsy may result from weakness)

In addition, bilateral CN VII palsy may result from congenital conditions (Möbius syndrome), sarcoidosis, Guillain-Barré syndrome, or neurofibromatosis type 2 (bilateral acoustic neuromas). GSPN = greater superficial petrosal nerve. (Illustration by Christine Gralapp.)

Any aberrant facial movements at rest or during volitional movement should be noted (see Fig 11-4). After any facial neuropathy, but most commonly as a result of Bell palsy, regenerating axons may reinnervate different muscles from those originally served; such aberrant regeneration can cause synkinetic movements. In this situation, the involved facial muscles may remain weak. When axons originally destined for the orbicularis oculi reinnervate the lower facial muscles, each blink may cause a twitch of the corner of the mouth or a dimpling of the chin. Conversely, movements of the lower face—such as pursing the lips, smiling, or chewing with the mouth closed—may produce involuntary eyelid closure.

Other disorders of aberrant facial innervation include lacrimation caused by chewing (*crocodile tears*), in which fibers originally supplying mandibular and sublingual glands reinnervate the lacrimal gland by way of the greater superficial petrosal nerve. This syndrome usually develops after severe injury to the proximal CN VII and may be accompanied by decreased reflex tearing and decreased ability to taste from the anterior two-thirds of the tongue.

Seventh Cranial Nerve Disorders

Disorders of Underactivity of the Seventh Cranial Nerve

Facial weakness or paralysis may occur with supranuclear, nuclear, or infranuclear lesions (Table 11-3).

Supranuclear lesions

A frontal lesion in the facial portion of the precentral gyrus results in a contralateral paralysis of volitional facial movement, which involves the lower face more severely than the upper face (upper motor neuron lesion). Emotional and reflex facial movements such

Table 11-3 Etiologies of Facial Paralysis**Idiopathic (Bell palsy)****Infections**

Acute or chronic otitis media

Herpes zoster (Ramsay Hunt syndrome)

Lyme disease

Other: diphtheria, enterovirus, human immunodeficiency virus, infectious mononucleosis, leprosy, meningitis, mumps, rubella, syphilis, tetanus, tuberculosis, varicella, zygomycosis**Miscellaneous**

Congenital facial paralysis

Diabetes mellitus

Guillain-Barré syndrome

Melkersson-Rosenthal syndrome

Sarcoidosis

Vasculitis

Polyarteritis nodosa

Wegener granulomatosis (granulomatosis with polyangiitis)

Neoplasms

Cerebellopontine angle tumor

Intratemporal bone tumor

Parotid gland tumor

Pontine glioma

Other: epidermoids, hemangioma, histiocytosis X, leukemia, lymphoma, sarcoma**Pontine demyelination****Pontine infarct or hemorrhage****Trauma**

as smiling and spontaneous blinking are usually preserved because they are controlled through extrapyramidal pathways.

With extrapyramidal disorders, such as parkinsonism or progressive supranuclear palsy, spontaneous facial expression is minimal, and the spontaneous blink rate is usually reduced. Volitional facial movements generally remain intact.

Brainstem lesions

Ipsilateral facial weakness that involves both the upper and lower face may occur with a pontine disorder. Vascular lesions and intraparenchymal tumors are the most common causes. Other evidence of a pontine disturbance is to be expected, such as ipsilateral corneal and facial anesthesia, CN VI palsy, lateral gaze palsy, cerebellar ataxia, and contralateral hemiparesis. Dissociations between the autonomic, sensory, and CN VII motor functions may be present. Large lesions of the pons may produce facial diplegia, which also occurs in Möbius syndrome, a congenital disorder involving bilateral CN VI palsies or gaze palsies.

Peripheral lesions

Peripheral or lower motor neuron lesions that result in ipsilateral facial weakness may have numerous causes. Concomitant impairment of CN V, CN VI, or CN VIII or cerebellar signs may indicate cerebellar pontine angle tumors.

Bell palsy, which typically occurs in adults, represents the most common type of facial neuropathy, but it must remain a diagnosis of exclusion. Bell palsy is characterized by the sudden onset of facial paresis. Pain may either precede the palsy or occur concurrently. Patients with Bell Palsy may report facial numbness, although their cutaneous sensation is usually intact. These patients may also note decreased tearing, diminished taste, and dysacusis.

Although the etiology of Bell palsy is unknown, it is believed to be caused by autoimmune or viral-induced inflammatory or ischemic injury with swelling of the peripheral nerve. The incidence of Bell palsy is higher in pregnant women and in patients with diabetes mellitus or a family history of Bell palsy. If the facial weakness progresses over a period of more than 3 weeks, an alternative etiology should be considered (eg, a neoplastic process, inflammatory disorder such as sarcoidosis, or an infectious cause).

Approximately 85% of patients with Bell palsy experience a satisfactory recovery, although subtle signs of aberrant regeneration can be detected on examination. In these patients, recovery typically begins within 3 weeks of onset of the deficit and is complete by 2–3 months. In the remaining patients, recovery is incomplete, and significant synkinesis with co-contraction of a variety of facial muscles is common. Complete facial palsy at the time of presentation, impairment of lacrimation, dysacusis, pregnancy, diabetes mellitus, and advanced age are all poor prognostic factors.

Corticosteroids are commonly used to treat Bell palsy, and evidence from meta-analyses and randomized trials supports their efficacy. A 7–10-day course of oral corticosteroids is recommended for patients without systemic contraindications within the first 72 hours. The addition of an antiviral medication (eg, acyclovir, famciclovir, or valacyclovir) is of unclear benefit.

Neoplasms may involve CN VII in the cerebellopontine angle (eg, acoustic neuroma [Fig 11-9], meningioma), within the fallopian canal, or in the parotid gland. Such lesions may compress CN VII, resulting in facial synkinesis. Most of these lesions are best evaluated through magnetic resonance imaging (MRI) with intravenous contrast.

Various infectious agents can cause CN VII pathology. The nerve may be impaired from meningitis. Lyme disease, caused by the tick-borne spirochete *Borrelia burgdorferi*,

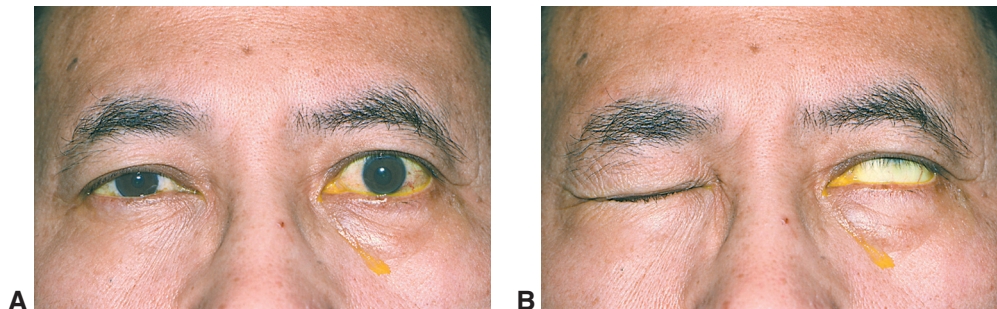


Figure 11-9 Facial nerve palsy. This 60-year-old patient experienced ocular irritation on the left side after excision of a left acoustic neuroma. **A**, The left eye will not close due to weakness of the left orbicularis oculi. **B**, Fortunately, corneal sensation remains intact, and the patient demonstrates an excellent Bell phenomenon. (Courtesy of Steven A. Newman, MD.)

can cause unilateral or bilateral facial palsies. Classic manifestations include a characteristic rash, arthritis, and meningopolyneuritis (see Chapter 14). The prognosis for CN VII palsy recovery following treatment of Lyme disease is excellent.

Herpes zoster that involves CN VII is called *Ramsay Hunt syndrome*. It is diagnosed through the identification of vesicles along the posterior aspect of the external auditory canal, over the tympanic membrane, or on the pinna. Pain is often severe, and postherpetic neuralgia may result. The prognosis for recovery is less promising than for Bell palsy. An isolated CN VII palsy, as well as other isolated or multiple CN palsies, may be the first sign of human immunodeficiency virus (HIV) seroconversion. Infectious disorders such as otitis media may spread to involve CN VII.

CN VII is the most common CN involved in sarcoidosis (see Chapter 14). The site of involvement is usually the parotid gland, which develops noncaseating granulomatous inflammation. CN VII involvement is frequently bilateral yet asymmetric.

Facial diplegia may occur in *Guillain-Barré syndrome*, especially in the variant *Miller Fisher syndrome*, when ophthalmoplegia and ataxia are also present. Cerebrospinal fluid analysis reveals an elevated protein level with a normal cell count, and deep tendon reflexes are usually absent. A high percentage of patients with Miller Fisher syndrome have anti-GQ1b IgG antibodies in their serum. Recovery is generally complete, and the serologic test results improve with clinical improvement.

CN VII palsy may occur from head trauma. The *Battle sign* (ecchymosis over the mastoid area) may be present and is associated with fractures of the temporal bone. Congenital facial palsy is frequently related to birth trauma from use of forceps and tends to resolve.

In *Melkersson-Rosenthal syndrome*, recurrent unilateral or bilateral facial paralysis is accompanied by chronic facial swelling and lingua plicata (furling of the tongue). The etiology of this disorder, which usually begins in childhood or adolescence, is unknown. The facial swelling is frequently marked and may be bilateral, even when facial paresis is only unilateral.

Given the extensive differential diagnosis for CN VII weakness, etiologic considerations in specific clinical situations deserve emphasis. *Bilateral* CN VII palsies are most frequently due to sarcoidosis, basilar meningitis (bacterial, viral, spirochetal), or Guillain-Barré syndrome. *Recurrent unilateral* CN VII involvement is most commonly idiopathic but may be caused by diabetes mellitus, Lyme disease, or Melkersson-Rosenthal syndrome. *Progressive* CN VII palsy is highly suggestive of a neoplastic etiology, either from tumor invasion (eg, brainstem, cerebellopontine, or parotid gland) or diffuse infiltration (eg, meningeal carcinomatosis). Further, accompanying CN palsies will aid in topographic localization of the lesion.

Schwartz SR, Jones SL, Getchius TS, Gronseth GS. Reconciling the clinical practice guidelines on Bell's palsy from the AAO-HNSF and the AAN. *Neurology*. 2014;82(21):1927–1929.

Treatment options for seventh cranial nerve underactivity

In cases of orbicularis oculi involvement, treatment of corneal exposure may be necessary. Artificial tear preparations and lubricants are sufficient in mild cases. Taping the eyelid shut with lubricating ointment in the eye for sleep may be necessary. Moisture chambers

have been used at night. Patients should be advised to avoid dusty and windy environments. Breakdown of corneal epithelium indicates the need for punctal plugs, tarsorrhaphy, or the injection of botulinum toxin to induce ptosis.

In patients with CN VII palsy, it is crucial to determine the status of CN V. Loss of corneal sensation combined with CN VII palsy is a particularly difficult clinical problem. The risk of combined neurotrophic and neuromyolytic keratitis warrants an aggressive approach, possibly including early tarsorrhaphy or an eyelid weight implant.

The simplest and most successful surgical treatment for corneal problems associated with chronic CN VII palsies is the implantation of gold or platinum eyelid weights, combined with horizontal eyelid tightening such as a lateral tarsal strip. To avoid the implantation of too small a weight, preoperative evaluation should include trials of various weights taped to the eyelid surface. The heaviest weight that can be lifted clear of the visual axis should be chosen. Later, if facial nerve function recovers, the weight can be removed.

Sohrab M, Abugo U, Grant M, Merbs S. Management of the eye in facial paralysis. *Facial Plast Surg.* 2015;31(2):140–144.

Disorders of Overactivity of the Seventh Cranial Nerve

Disorders of CN VII, its nucleus, or the pyramidal or extrapyramidal pathways may produce hyperexcitable states. Benign essential blepharospasm (BEB), hemifacial spasm, and facial myokymia are the 3 most common disorders of overactivity (Table 11-4).

Benign essential blepharospasm

BEB is a bilateral condition that consists of episodic contraction of the orbicularis oculi. Onset usually occurs between the ages of 40 and 60 years. Initially, the spasms are mild and infrequent, but they may progress to the point that the patient's daily activities are severely disrupted. In advanced cases, the patient's eyelids cannot be pried open during an episode of spasm. Facial grimacing and other movements may be associated with the blepharospasm (*Meige syndrome*, Fig 11-10), and cogwheeling in the neck and extremities or other extrapyramidal signs may be noted. *Tardive dyskinesia* secondary to neuroleptic and antipsychotic drugs can produce spasms that involve the mouth. Extrapyramidal disorders such as parkinsonism, Huntington disease, and basal ganglia infarction may be accompanied by some degree of blepharospasm.

Although the exact cause of BEB is unknown, increasing evidence acquired through functional neuroimaging suggests that it is caused by basal ganglia dysfunction. The clinician evaluating a patient with blepharospasm should exclude causes of reflex blepharospasm, in particular severe dry eye, intraocular inflammation, and meningeal irritation (usually associated with photophobia). Stress may exacerbate the condition. Neuroradiologic studies are generally unrevealing and rarely indicated.

The efficacy of medical therapy for BEB is generally limited. Tinted lenses, such as those with an FL-41 tint, may improve blink frequency and light sensitivity. The treatment of choice is injection of botulinum toxin (onabotulinumtoxinA, incobotulinumtoxinA, abobotulinumtoxinA, or rimabotulinumtoxinB) into the orbicularis oculi muscle. Because

Table 11-4 Comparison of the Common Causes of CN VII Overactivity

	Laterality	Site of Dysfunction*	Etiology	Treatment
Benign essential blepharospasm	Bilateral	Basal ganglia	Unknown	Botulinum toxin injections (preferred treatment) <i>Medical:</i> Haloperidol, clonazepam, other drugs <i>Surgical:</i> Extirpation of eyelid protractors, selective CN VII section
Hemifacial spasm	Unilateral	Facial root in cerebellopontine angle	Nerve compression by blood vessel or tumor	Botulinum toxin injections (preferred treatment) <i>Medical:</i> Carbamazepine, baclofen, other drugs <i>Surgical:</i> Microsurgical decompression of facial root
Eyelid myokymia	Unilateral	Unknown	Unknown	Reassurance, botulinum toxin injections
Facial myokymia	Unilateral	Facial nucleus or fascicle in pons	Glioma, multiple sclerosis	Treatment of the underlying cause <i>Medical:</i> Carbamazepine, phenytoin, or botulinum toxin injections

*Presumed.

Figure 11-10 Benign essential blepharospasm with Meige syndrome. This patient has contraction of the orbicularis oculi muscles in association with facial grimacing. (Courtesy of Eric Eggenberger, DO.)



the effect of the toxin is temporary, lasting only a few months, repeat injections are necessary. The efficacy of the drug relates to its ability to cause muscle weakness. Complications such as ptosis, local ecchymosis, ectropion, diplopia, lagophthalmos, and exposure keratopathy are usually mild and transient. Treatment typically consists of 4–8 injection sites per periorbital area. The central portion of the pretarsal orbicularis oculi muscle should be avoided to minimize the chance of inducing ptosis.

Treatment with surgical myectomy is reserved for patients who are refractory to botulinum toxin injection. Treatment failure can be seen in patients with pure blepharospasm but is more commonly seen in patients with blepharospasm associated with apraxia of eyelid opening. See BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*, for a more extensive discussion on surgical myectomy.

BEB may cause psychological distress, with some patients withdrawing socially as the symptoms worsen. Thus, counseling may be as valuable as the medical and surgical management of this condition. The Benign Essential Blepharospasm Research Foundation (www.blepharospasm.org) aids research efforts and provides education and support to blepharospasm patients.

Ross AH, Elston JS, Marion MH, Malhotra R. Review and update of involuntary facial movement disorders presenting in the ophthalmological setting. *Surv Ophthalmol*. 2011; 56(1):54–67.

Hemifacial spasm

Hemifacial spasm is characterized by unilateral episodic spasms that involve the facial musculature and typically last from a few seconds to minutes. The disorder frequently begins as intermittent twitching of the orbicularis oculi muscle but, over the course of several years, spreads to involve all the facial muscles on 1 side (Fig 11-11). Episodes may increase in frequency for weeks to months and then abate for months at a time. CN VII function is usually intact, although, over time, subtle ipsilateral facial weakness may develop. Unlike BEB, the spasms can occur during sleep.

The pathogenesis of hemifacial spasm is most commonly compression of the CN VII root exit zone by a dolichoectatic vessel. Abnormal firing in the motor nucleus or ephaptic



Figure 11-11 Hemifacial spasm. This 73-year-old woman has intermittent twitching involving the entire right side of the face. (Courtesy of Rod Foroozan, MD.)

transmission of nerve impulses causes innervation directed toward a particular muscle group to excite adjacent nerve fibers that are directed to another muscle group. Less commonly, tumors within the cerebellopontine angle, Bell palsy, previous injury to CN VII, or demyelination may lead to the spasms; therefore, MRI and magnetic resonance angiography (MRA) of the brain is typically performed to exclude a compressive lesion or other secondary causes.

Botulinum toxin injection into the periocular and facial muscles has proved very effective and is the treatment of choice for hemifacial spasm in most patients. Reinjection is required, at typical intervals of 3–4 months. Hemifacial spasm responds to lower doses of botulinum toxin than does blepharospasm.

Carbamazepine, clonazepam, or baclofen may provide improvement in some patients. Suboccipital craniectomy with placement of a sponge between CN VII and the offending blood vessel (*microvascular decompression*) may be considered for advanced cases or younger patients. Surgical decompression may offer a cure but carries higher risks than alternative treatments.

Yaltho TC, Jankovic J. The many faces of hemifacial spasm: differential diagnosis of unilateral facial spasms. *Mov Disord.* 2011;26(9):1582–1592.

Spastic paretic facial contracture

Spastic paretic facial contracture is a rare disorder characterized by unilateral facial contracture with associated facial weakness. Typically, it begins with myokymia of the orbicularis oculi muscle, which gradually spreads to most of the ipsilateral facial muscles. At the same time, tonic contracture of the affected muscles becomes evident. Over weeks to months, ipsilateral facial weakness develops, and voluntary facial movements of the affected side diminish. Spastic paretic facial contracture is a sign of pontine dysfunction in the region of the CN VII nucleus, often caused by a pontine neoplasm. Damage to the nucleus causes facial weakness, and involvement of supranuclear connections leads to facial spasticity.

Facial myokymia

Facial myokymia is characterized by continuous unilateral fibrillary or undulating contraction of facial muscle bundles. Occasionally, these rippling movements begin within a portion of the orbicularis oculi and may spread to involve most of the facial muscles.

Facial myokymia typically signifies intramedullary disease of the pons involving the CN VII nucleus or fascicle. It is usually the result of a pontine glioma in children and multiple sclerosis in adults. In rare instances, myokymia occurs in patients with Guillain-Barré syndrome. Myokymia may be relieved with carbamazepine, phenytoin, or injection of botulinum toxin.

Intermittent fluttering of the orbicularis oculi (*benign eyelid myokymia*) is relatively common. The phenomenon usually lasts for days or weeks. In rare cases, eyelid myokymia can last for months; these patients may benefit from an injection of botulinum toxin. Caffeine, stress, and sleep deprivation are common contributing factors.

Banik R, Miller NR. Chronic myokymia limited to the eyelid is a benign condition. *J Neuro-ophthalmol.* 2004;24(4):290–292.

Other conditions

In rare instances, focal cortical seizures are manifested by gross clonic movements involving only 1 side of the face. The eyes deviate away from the side of the seizure focus during the episode; the patient's ipsilateral hand may also have clonic movements. Frequently, *Todd paralysis*, a transient supranuclear facial paresis, follows the seizure, and the eyes may deviate toward the side of the prior seizure focus.

Oral facial dyskinesias (eg, tardive dyskinesia) are usually observed after long-term use of major tranquilizers and may persist even after the drugs are stopped. *Habit spasm* such as facial tic or nervous twitch is relatively common, particularly in childhood, and is characterized by involuntary, repetitive, reproducible facial movements that can be promptly inhibited on command. These movements tend to disappear in time without treatment. Only in rare cases does Tourette syndrome present with facial twitching alone.

Jung HY, Chung SJ, Hwang JM. Tic disorders in children with frequent blinking. *J AAPOS*. 2004;8(2):171–174.

The Patient With Head, Ocular, or Facial Pain

Head Pain

Headache is a common complaint presented to the ophthalmologist. When pain extends to the orbits, the patient and referring physician may assume that the eyes are in some way responsible for the discomfort. Often the patient may have fears, perhaps unspoken, of a brain tumor.

The most important part of an evaluation for headache is the patient's history, because in the vast majority of such patients, the results of the ocular examination are normal (Table 12-1).

In addition to receiving a complete ophthalmic examination, the patient reporting the headache should be screened systemically, including having measurements taken of blood pressure and pulse and undergoing neurologic examination for meningeal signs (eg, neck stiffness), focal tenderness, and integrity of cranial nerve (CN) function. Any reports of visual phenomena should prompt careful visual field testing.

The International Headache Society (IHS) classification scheme, which was designed in 1988 and revised in 2013, separates *primary* headaches (eg, migraine, tension-type, and trigeminal autonomic cephalgias) from *secondary* headaches (ie, headaches resulting from other causes).

Several clinical features of headache may suggest the need for neuroimaging and additional diagnostic testing. The “SNOOP” mnemonic is a useful tool for identifying the red flags of a potentially serious headache:

- Systemic symptoms (eg, fever, weight loss, or myalgias) or Secondary risk factors (immunosuppression or systemic cancer)
- Neurologic symptoms (eg, confusion, impaired alertness or consciousness, neck stiffness, or association of headache with physical exertion or change in body position) or signs (eg, papilledema, CN III palsy, or homonymous visual field defects)
- Onset: sudden, abrupt, or split-second
- Older: new onset and progressive headache, especially in patients 50 years or older
- Previous headache history: first headache or different (change in attack frequency, severity, or clinical features)

Table 12-1 Important Clinical Points of a Patient’s Headache History

Nature of the headache (sharp or dull, throbbing or constant, “squeezing”)
Location of the headache (unilateral or bilateral, localized or diffuse)
Daily pattern of headache (worse in the morning or later in the day, waking the patient from sleep)
Overall pattern (when headaches began, chronicity, recent change in pattern)
Precipitating or alleviating factors (supine position, bending over, coughing, foods)
Associated phenomena (scintillating scotomata, flashing lights, photophobia, transient visual loss, transient diplopia, nausea or vomiting, vertigo, ptosis, tearing, paresthesias, weakness, tinnitus)
Family history of headaches

Table 12-2 summarizes the diagnosis and management of some common headache and related facial pain syndromes.

Giant cell arteritis (GCA) or temporal arteritis should be suspected in patients older than 50 years with new headaches. Symptoms of this condition also include jaw claudication, fever, weight loss, scalp tenderness, polymyalgia, fatigue, and visual symptoms. Westergren erythrocyte sedimentation rate (ESR; Westergren method) and C-reactive protein testing can help screen such patients, but a normal ESR test result does not exclude a diagnosis of GCA (see Chapter 14). Tenderness over the temporal artery (particularly if the artery is enlarged or nodular) may support the diagnosis and indicate the region of greatest yield for a biopsy.

Headache caused by *elevated intracranial pressure*, as with intracranial mass lesions or idiopathic intracranial hypertension, is typically global, constant, and worse in the morning. Bending over or moving the head often worsens pain, as does Valsalva maneuver from coughing and straining. Vomiting may occur even without nausea. Other focal, non-localizing neurologic signs such as CN VI palsy or papilledema may be present. Pulsatile tinnitus and transient visual loss are common associated symptoms.

A sudden severe headache accompanied by neck stiffness, change in mentation, or focal neurologic signs suggests *intracranial hemorrhage*. Neuroimaging is urgently required in such cases.

Headache caused by meningitis may be chronic and not associated with focal neurologic deficits. Neck stiffness and pain on flexion, back pain, pain on eye movement, and photophobia may suggest meningeal inflammation.

Dodick DW. Clinical clues and clinical rules: Primary vs secondary headache. *Adv Stud Med.* 2003;3(6C):S550–S555.

Ducros A, Biousse V. Headache arising from idiopathic changes in CSF pressure. *Lancet Neurol.* 2015;14(6):655–668.

Friedman DI, Digre KB. Headache medicine meets neuro-ophthalmology: exam techniques and challenging cases. *Headache.* 2013;53(4):703–716.

Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 3rd ed. *Cephalalgia.* 2013; 33(9):629–808.

Migraine and Tension-type Headache

Migraine is a common disabling primary headache disorder consisting of repetitive bouts of headache. Approximately 6%–8% of men and 15%–18% of women in North America and Europe experience migraine annually. A familial tendency for migraine is strong,

Table 12-2 Diagnosis of Facial Pain

Characteristics	Classic Trigeminal Neuralgia	Symptomatic Trigeminal Neuralgia	Cluster Headache	Episodic or Chronic Paroxysmal Hemicrania	SUNCT Syndrome	Hemicrania Continua
Age/Gender Ratio	Middle-aged or later/M:W 1:4	Any/M=W	Any/M:W 9:1	Any/M:W 1:3	Any/M:W 8:1	Any/W > M
Side and Location of Pain	Unilateral	May be bilateral	Unilateral periorbital	Unilateral periorbital	Unilateral periorbital	Unilateral
Type of Pain	Stabbing	V_1 , V_2 , or V_3	Boring, very severe	Very severe	Very severe	hemicrania
Duration of Pain	<1 second	Chronic	15–180 minutes	2–30 minutes	5–240 seconds	Sharp pain
Temporal Profile	Few to many per day for a few weeks or months; pain-free between attacks	Fluctuations, but no remission	1–8 per day Attack phase: 4–16 weeks Remission: 6 months–2 years	5 per day	Numerous in a day; sometimes dull pain between attacks; remissions with irregular pattern	<1 minute Associated with continuous headache Fluctuating intensity
Associated Signs	None; look for trigger	Hypoesthesia V_1 , dysesthesia V_1 , motor deficit V_1 , other cranial nerve palsies	Horner syndrome, eye redness, tearing, rhinorrhea	Horner syndrome, eye redness, tearing, rhinorrhea	Eye redness, tearing	Nausea, vomiting, photophobia $\pm$ Horner syndrome
Interictal Examination	Normal	Hypoesthesia V_1 , motor deficit V_1	Normal $\pm$ permanent Horner syndrome	Normal $\pm$ permanent Horner syndrome	Normal	Normal
Specific Treatment	Carbamazepine	Variable response	Acute: oxygen, injectable or intranasal triptans, and DHE Chronic: lithium, steroids, calcium channel inhibitors	Indomethacin stops pain	None Variable response	Indomethacin

DHE = dihydroergotamine mesylate; SUNCT = short-lasting unilateral neuralgiform headache with conjunctival injection and tearing; V = trigeminal nerve; M = men; W = women.

Adapted from Biousse V, Newman NJ. *Neuro-Ophthalmology Illustrated*. 2nd ed. New York: Thieme; 2015: 545.

and the patient may report having had motion sickness as a child. Onset of migraine may be linked to times of hormonal change, such as during puberty or young adulthood, and migraine episodes may decrease after menopause. Support for a diagnosis of migraine includes the unilaterality or pulsating character of the pain and associated symptoms such as nausea or vomiting, photophobia, phonophobia, and aggravation of pain with routine physical activity. Migraine may be exacerbated by menstruation, pregnancy, hunger, stress, certain foods (eg, chocolate or wine), and sleep deprivation.

Migraine without aura

Migraine without aura, which comprises 65% of all migraine, has no preceding neurologic symptoms. This type of headache may be global, asymmetric bilateral, or unilateral and can last hours to days. Distinguishing between it and the very common tension-type headache (see the section “Tension-type headache”) may be challenging.

Migraine with aura

Migraine with aura, which comprises 30% of all migraines, is heralded by neurologic symptoms that are most commonly visual. Because they originate from the occipital lobes as a result of cortical spreading depression, visual symptoms in migrainous aura are *always* binocular (although the patient may report them as monocular in the eye that has the symptom in the temporal visual field). The aura builds over minutes, with positive visual phenomena that typically have movement. The classic *scintillating scotoma with fortification spectrum* commonly begins with a small scotoma that gradually expands into the peripheral vision (Fig 12-1). The scotoma is bounded by a zigzag, shimmering, colorful, or

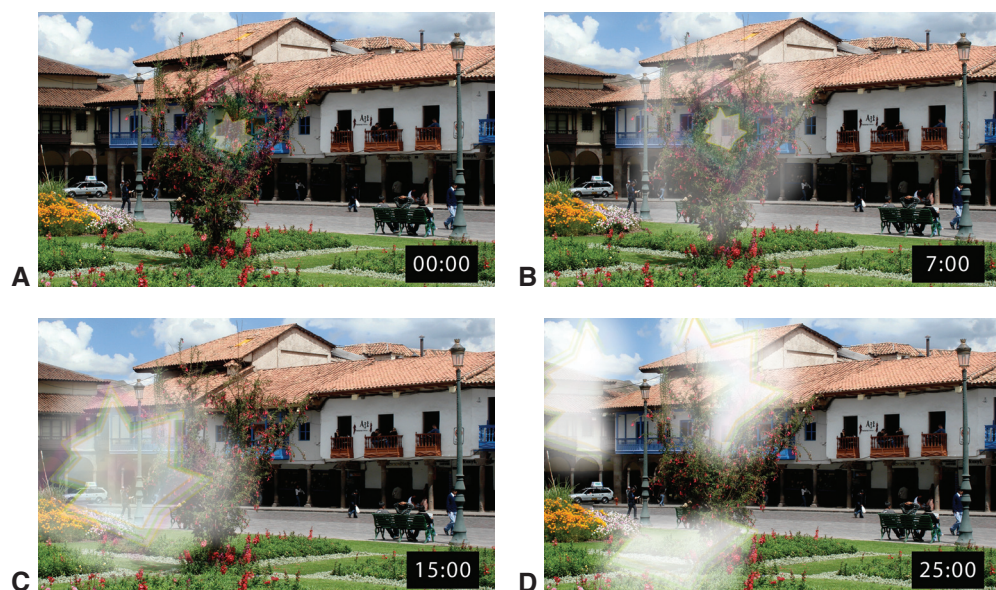


Figure 12-1 Visual aura of migraine. **A**, The aura commonly begins with a small scotoma near fixation that gradually expands into the peripheral vision (**B–C**) and then breaks up (**D**). The times shown represent minutes from the onset of the visual aura. (Courtesy of Julie Falardeau, MD.)

silvery image that moves temporally into the periphery and then breaks up. Loss of vision may occur, and the presence of both positive and negative phenomena is the hallmark of migraine aura. The aura typically lasts between 5 and 60 minutes and is usually followed by a contralateral throbbing headache. The aura always completely resolves. Most patients experience associated nausea, photophobia, and phonophobia. When untreated, migraine attacks typically last from 4 hours to 72 hours.

Studies of migraine pathophysiology have found evidence for primary dysfunction involving the afferent sensory neurons of CN V. Activation of the trigeminal nucleus caudalis is thought to cause the release of vasoactive chemokines at the vascular endings of CN V. These neuropeptides are thought to cause dilation of the pial arteries, increase vascular permeability, and induce an inflammatory response that activates trigeminal afferent fibers within the walls of blood vessels.

Genetic factors with a substantial familial incidence (eg, familial hemiplegic migraine, a rare autosomal dominant form of migraine) have suggested that increased neuronal excitability is a primary event in migraine. This condition may underlie the spreading depression in the occipital region thought to be responsible for the visual aura and the blood vessel changes that result in pain, as well as the brainstem or bilateral hemispheric symptoms of basilar-type migraine.

Typical aura without headache

Some patients may report only the visual symptoms of migraine aura, without an associated headache. This typical aura without headache, previously termed *acephalgic migraine* comprises 5% of all migraines and must be differentiated from transient ischemic attacks (TIAs). Typical aura without headache mainly occur in adults with a prior history of migraine with aura. The typical manifestation of migraine aura is scintillating scotoma and, less commonly, transient homonymous hemianopia without positive visual phenomena or peripheral visual field constriction that progresses to tunnel vision or complete vision loss. Symptoms typically last 5–60 minutes and always completely resolve. A patient experiencing positive visual phenomena or a family history of migraine with aura is helpful for diagnosis, as is the presence of the classic scintillating scotoma with fortification spectrum. The absence of these features or the presence of residual visual field defects or a bruit should raise suspicion of another underlying process, such as cerebrovascular disease or a vascular malformation, and prompt urgent brain imaging.

Evaluation of patients with migraine

If the patient has a typical history of migraine and the results of neurologic and ophthalmic examination are normal, neuroimaging studies are unlikely to show an intracranial abnormality. A history of visual phenomena and hemicranial headaches on both sides suggests a benign etiology. Although symptoms that occur strictly on one side are more worrisome, patients with this clinical presentation are also likely to have migraine. Occasionally, a mass lesion or a large vascular malformation is heralded by typical migraine symptoms, but in such cases, there are often residual visual field defects (Fig 12-2; see also Chapter 14). Such a finding underlines the importance of visual field testing in the evaluation of patients with presumed migrainous visual aura. Referral of patients with suspicious

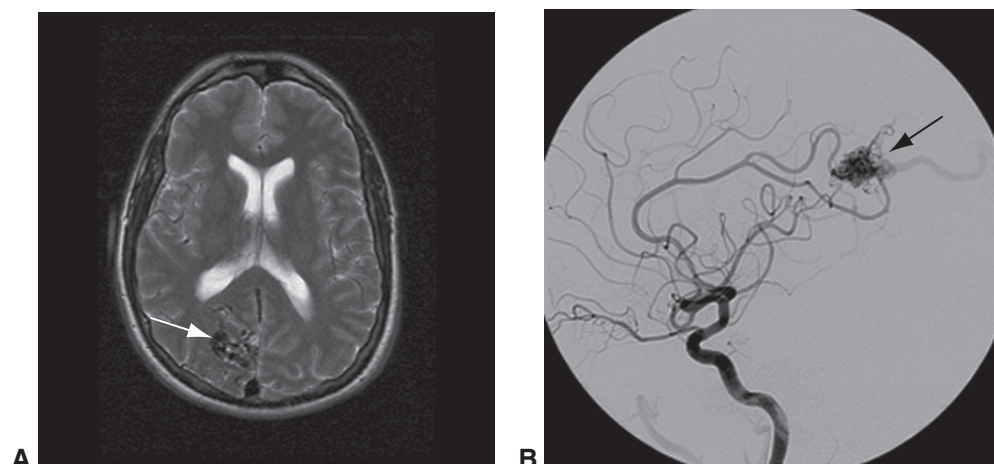


Figure 12-2 Occipital lobe arteriovenous malformation. **A**, T2-weighted axial magnetic resonance imagery (MRI) shows an irregular hypointense mass (arrow) suggestive of a vascular lesion within the right occipital lobe. **B**, Lateral-projection cerebral arteriogram confirms that the lesion is an arteriovenous malformation (arrow). (Courtesy of Rod Foroozan, MD.)

headaches to a neurologist is prudent. The following findings may suggest the need for additional evaluation of those patients presumed to have migraine:

- Headache or aura always occurring on the same side
- Headache preceding the aura
- Neurologic deficit, including visual field defect, persisting after aura resolves
- Atypical aura (more than 1 aura occurring in a single day, lack of expansion of or change in aura, duration less than 5 minutes or more than 60 minutes)

Frishberg BM, Rosenberg JH, Matchar DB, et al; for the US Headache Consortium. Evidence-based guidelines in the primary care setting: neuroimaging in patients with nonacute headache. American Academy of Neurology website. Available at <http://tools.aan.com/professionals/practice/pdfs/gl0088.pdf>. Accessed January 13, 2017.

Tension-type headache

Tension-type headaches are chronic, described as aching or viselike, typically worse at the end of the day, and often precipitated by stress. They are not associated with typical auras. The specific pathophysiology and treatment of tension-type headaches remain unclear. Such headaches may be associated with depression.

Treatment of migraine and tension-type headache

The specific type of headache and the needs of the patient should guide treatment. Some patients, for example, need only reassurance that they do not have serious intracranial disease. Precipitating or contributing factors should be eliminated as much as possible. Certain foods provoke headaches in some people, and patients should consider avoiding the potential triggers of chocolate, nitrates, monosodium glutamate, aged cheese, caffeine, wine and other alcoholic beverages, aspartame-based sweeteners, nuts, and shellfish. The role of estrogens and oral contraceptives is uncertain, but a temporal relationship between

initiation of hormone therapy and the development of migraine symptoms suggests a causal relationship.

Other environmental migraine triggers include stress or relief from stress, change in sleep patterns, fumes or strong scents such as perfumes and cigarette smoke, and exercise.

Migraine therapy consists of treatment for the acute symptoms as well as prophylactic management. For treatment of acute symptoms, various drugs can be used, including serotonin 5-HT_{1B/1D}-receptor agonists (triptans), nonsteroidal anti-inflammatory drugs (NSAIDs), dihydroergotamine, and other combination drugs that include caffeine (long-term caffeine intake, however, worsens headaches). An antiemetic drug may also be necessary. The triptans (eg, sumatriptan, rizatriptan, zolmitriptan, frovatriptan, and almotriptan) are useful for symptomatic relief of the migrainous headache but should be used cautiously in patients with migraine with aura and only after the aura resolves to avoid vasoconstriction-induced infarct. Though rare, these drugs can also cause myocardial infarction and are typically not used for patients with suspected or known coronary artery disease.

Analgesic medications should be prescribed with caution, and narcotics should be avoided. The use of analgesic medications for more than 15 days per month can lead to *analgesic rebound headache*, characterized by a constant headache that is relieved only with the continuous use of pain medications. Therefore, obtaining a thorough medication history from patients with headache is important. Treatment of analgesic rebound headaches requires the withdrawal of analgesics, and hospitalization may be needed. *Prophylactic* treatment is warranted if headaches disrupt activities of daily living beyond what the patient is willing to tolerate. Topiramate, an antiepileptic γ -aminobutyrate (gamma-aminobutyric acid, or GABA) agonist, has been increasingly prescribed for patients with migraine. However, a syndrome characterized by acute myopic shift, ciliochoroidal effusion, and acute bilateral angle-closure glaucoma can occur in some patients using topiramate (see BCSC Section 10, *Glaucoma*).

Alternatively, beta-blockers, calcium channel blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), sodium valproate, and gabapentin may be used as prophylactic drugs, as may NSAIDs if their potential for causing analgesic rebound headaches is kept in mind. Oral administration of magnesium and riboflavin can be effective for some patients, as well as pericranial botulinum toxin injections. Tension-type headaches are more likely to respond to treatment with tricyclic antidepressants, topiramate, gabapentin, muscle relaxants, and NSAIDs, although the overall rate of success with such drugs is not as high as for migraine. Various forms of biofeedback may be helpful.

Burstein R, Nosedá R, Borsook D. Migraine: multiple processes, complex pathophysiology.

J Neurosci. 2015;35(17):6619–6629.

Couch JR. Update on chronic daily headache. *Curr Treat Options Neurol.* 2011;13(1):41–55.

Monteith TS, Goadsby PJ. Acute migraine therapy: new drugs and new approaches. *Curr Treat Options Neurol.* 2011;13(1):1–14.

Trigeminal Autonomic Cephalgias and Hemicrania Continua

The trigeminal autonomic cephalgias (TACs) include cluster headache, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks with conjunctival

injection and tearing (SUNCT). The TACs are primary headache disorders characterized by short-lasting unilateral head pain that occurs with ipsilateral cranial autonomic findings. They can be difficult to treat and are best managed by neurologists.

Cluster headache is 3–4 times as common in men as in women. Although the typical age of onset is in the second and third decades of life, it can occur at any age and is typically precipitated by alcohol use. Cluster headache is characterized by excruciating bouts of pain lasting 15 minutes to 180 minutes and localized behind one eye in the distribution of the ophthalmic division of CN V (V_1). Associated features include ipsilateral tearing, conjunctival injection, rhinorrhea, and transient (although it can become permanent) postganglionic Horner syndrome. The pain may wake the patient from sleep and cause restlessness. Headaches occur in clusters of episodes over days or weeks, typically beginning like clockwork at the same time of day, then remit for months or years, suggesting that the hypothalamus may play a role in the pathogenesis. Cluster headaches can be difficult to treat. Abortive drugs include subcutaneous or intranasal triptans, inhaled oxygen, dihydroergotamine, and intranasal lidocaine. Verapamil, lithium, methysergide, corticosteroids, topiramate, and gabapentin can be useful for prophylaxis.

Paroxysmal hemicrania is characterized by short, severe attacks of pain with cranial autonomic features that occur several times daily. The headache typically lasts between 2 minutes and 30 minutes but may persist for hours. A dramatic resolution of the headache occurs with indomethacin administration.

SUNCT is characterized by unilateral orbital or temporal pain that is severe and throbbing or stabbing. The headache typically occurs more than 20 times per day, lasts 5 seconds to 240 seconds, and is often associated with conjunctival injection and tearing.

Unlike the other TACs, hemicrania continua is characterized by a continuous unilateral headache of variable intensity that waxes and wanes without disappearing completely. The forehead, temple, orbit, and occiput are common sites of pain. Autonomic symptoms are present in most patients. This primary headache disorder is also responsive to treatment with indomethacin.

Idiopathic Stabbing Headache

Also known as “ice pick headache” and “jabs and jolts syndrome,” idiopathic stabbing headache manifests as episodic, momentary, sharp, jabbing pains and occurs more commonly in patients with migraine than in those with other types of headaches. Patients with cluster headaches also have a high incidence of idiopathic stabbing headache, typically occurring in the same area as the cluster pain. The most common location for such headaches is in the distribution of V_1 , particularly the orbit, and less commonly the parietal, temporal, facial, occipital, and retroauricular regions. The pain may last less than a second or may occur as a series of stabbing sensations. Idiopathic stabbing headache often responds to indomethacin administration, and many patients improve with standard prophylactic headache drugs.

Inherited Encephalopathies Resembling Migraine

Mitochondrial myopathy and encephalopathy, lactic acidosis, and strokelike episodes (MELAS) is a hereditary mitochondrial disorder occurring in children and young adults. Its symptoms (headache, nausea, vomiting, transient hemianopia, and hemiparesis) suggest

migraine, but permanent neurologic disturbance occurs with spongiform cortical degeneration. Serum and cerebrospinal fluid (CSF) lactate levels are elevated, and hyperintense lesions may be observed on T2-weighted magnetic resonance imaging (MRI) of the temporal, parietal, and occipital lobes.

Headache resembling migraine may also occur as the initial symptom of *cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy* (CADASIL), an autosomal dominant angiopathy that is associated with a mutation in the *NOTCH3* gene on chromosome 19. Headaches occur in 30%–40% of patients with CADASIL and often arise later in life than typical migraine. Recurrent lacunar strokes with neurologic deficits and cognitive decline eventually occur. Widespread leukoencephalopathy, particularly within the temporal and frontal lobes, is apparent on MRI.

Boussier MG, Biousse V. Small vessel vasculopathies affecting the central nervous system. *J Neuroophthalmol*. 2004;24(1):56–61.

Ocular and Orbital Pain

There is a popular misconception that “eye strain” due to refractive errors and strabismus is a common cause of eye and head pain. Although refractive errors and strabismus should be corrected as appropriate, and such corrections may ameliorate pain, ocular or orbital pain has many more potentially serious causes. The eye is heavily innervated by sensory nerve fibers (see Chapter 1), and inflammatory, ischemic, and even neoplastic involvement of the eye and orbit can produce pain. True ophthalmic causes of eye pain include dry eye and other forms of keratitis, acute angle-closure glaucoma, and intraocular inflammation. These conditions are most commonly diagnosed through examination of the cornea, anterior segment, and anterior vitreous using a slit lamp. In addition, periocular pain may be referred facial pain (see the section Facial Pain).

Dry eye is a very common cause of ophthalmic discomfort (See Chapter 3 in BCSC Section 8, *External Disease and Cornea*). Exacerbated by visual tasks that decrease blink frequency, especially those involving long periods of computer use, it has various causes and results from conditions that either decrease tear production or increase tear evaporation. Pain on awakening may be related to recurrent corneal erosion syndrome.

Causes of ocular pain that are unrelated to keratitis include acute angle-closure glaucoma, which may be confirmed with gonioscopy and intraocular pressure measurements. Scleritis is usually accompanied by ocular tenderness. Posterior segment examination with indirect ophthalmoscopy or slit-lamp biomicroscopy may reveal evidence of choroidal or retinal inflammation or posterior scleritis. These causes of ocular pain are discussed in more detail in BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*, and Section 9, *Uveitis and Ocular Inflammation*.

Orbital inflammation or infection (*orbital cellulitis*) usually produces severe eye pain or pain on eye movement, variably accompanied by ocular motility abnormalities, eyelid edema, and proptosis (see BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*). Peri-orbital pain may be the initial manifestation of inflammation or thrombosis within the cavernous sinus. Pain with eye movement commonly accompanies an *inflammatory or demyelinating optic neuropathy* (see Chapter 4), often in association with decreased vision,

visual field changes, and a relative afferent pupillary defect (RAPD). Rapidly expanding tumors of the orbit, orbital apex, and cavernous sinus may also produce eye pain. In these cases, other signs will likely be present, such as a visual field defect, proptosis, ocular motility deficit, resistance to retropulsion of the globe, an RAPD, or an abnormal optic nerve appearance. Microvascular cranial neuropathies (CN III, IV, or VI) can cause retro-orbital pain, with associated abnormal ocular motility.

Occipital neuralgia, which is discussed later in this chapter, produces pain and tenderness over the greater occipital nerve that radiates to the ipsilateral eye area.

Trochlear Headache and Trochleitis

Trochlear headache, or trochleitis, is an underdiagnosed orbital cause of headache. Patients with this condition typically present with a history of months to years of chronic orbital pain. Inflammation of the trochlea causes localized pain, swelling, and tenderness, and there may be associated limitation of eye movement. When there is no obvious orbital inflammation, the diagnosis can be made by eliciting pain with palpation of the involved trochlea. The etiology is usually idiopathic, but trochleitis can be associated with systemic autoimmune diseases. This condition primarily (90%) occurs in women. Treatment includes local injection of corticosteroids in the region of the trochlea or high doses of NSAIDs.

Friedman DI, Gordon LK, Quiros PA. Headache attributable to disorders of the eye. *Curr Pain Headache Rep.* 2010;14(1):62–72.

Harooni H, Golnik KC, Geddie B, Eggenberger ER, Lee AG. Diagnostic yield for neuroimaging in patients with unilateral eye or facial pain. *Can J Ophthalmol.* 2005;40(6):759–763.

Levin LA, Lessell S. Pain: a neuro-ophthalmic perspective. *Arch Ophthalmol.* 2003;121(11):1633.

Photophobia

Photophobia occurs most frequently as a result of ocular inflammatory disorders, including keratitis and uveitis (particularly iritis), and less commonly from chorioretinitis, retinal degenerative disorders, and lesions along the course of the anterior or retrochiasmal visual pathway. Photophobia may also occur because of meningeal irritation (eg, meningitis, subarachnoid hemorrhage) or migraine and is commonly reported by patients with traumatic brain injury.

Katz BJ, Digre KB. Diagnosis, pathophysiology, and treatment of photophobia. *Surv Ophthalmol.* 2016; 61(4): 466–477.

Facial Pain

Patients may refer localized facial pain to the eye. Common sources of facial pain include dental disorders and sinus disease. Other facial pain syndromes include trigeminal neuralgia, glossopharyngeal neuralgia, temporomandibular joint (TMJ) syndrome, and herpes zoster neuralgia. The last can be associated with facial and/or auditory nerve involvement

in herpes zoster oticus or Ramsay Hunt syndrome. The onset of facial pain in an elderly patient may indicate GCA. Facial pain is occasionally a sign of nasopharyngeal carcinoma or perineural infiltration of skin cancer (squamous cell, basal cell, or melanoma) affecting the trigeminal nerve or dura at the base of the brain.

Trigeminal Neuralgia

Trigeminal neuralgia, also known as *tic douloureux*, typically occurs during middle age or later. It is essential to differentiate primary (classic) trigeminal neuralgia (no obvious cause and completely normal examination in between episodes) from secondary (symptomatic) trigeminal neuralgia, in which a lesion affecting the trigeminal nerve can be identified. In 80%–90% of cases, the neuralgia is caused by vascular compression of CN V, although secondary trigeminal neuralgia may also result from demyelinating disease, an infiltrative process, or a posterior fossa mass lesion. In primary trigeminal neuralgia, the pain is almost always unilateral (95%) and involves V₂ or V₃; involvement of V₁ alone is rare (<5%) and suggests a secondary cause. Chewing, tooth brushing, or a cold wind may precipitate paroxysmal burning or electric shock–like jabs, which last seconds to minutes. There may be periods of remission.

Sensory function in the face should be normal on testing in primary trigeminal neuralgia; hypoesthesia, anesthesia, or dysesthesia increases the likelihood of a secondary cause. These patients should have neuroimaging of the posterior fossa, preferably MRI. Treatment options include use of the medications gabapentin, pregabalin, carbamazepine, phenytoin, baclofen, clonazepam, and valproic acid; selective destruction of trigeminal fibers (rhizotomy); or surgical decompression of CN V in the posterior fossa.

Occipital Neuralgia

Paroxysmal stabbing pain in the distribution of the greater or lesser occipital nerves may be confused with other causes of head and facial pain. Tenderness may be elicited with pressure over the affected nerve. Injection of local anesthetic drugs relieves the pain and is helpful in confirming the diagnosis.

Temporomandibular Disease

Pain from the temporomandibular area may arise from either the joint or the muscle. Joint pain exacerbated by chewing or talking suggests joint disease. A click or pop with limited jaw opening may be present. Pain from the muscle is more difficult to diagnose, as it may be referred to the ear, preauricular area, or neck. Jaw pain or claudication in an elderly patient may be an early symptom of GCA.

Internal Carotid Artery Dissection

Internal carotid artery dissection typically produces pain localized to the face (see Chapter 14). It is often accompanied by ipsilateral sympathetic dysfunction (Horner syndrome) due to involvement of the sympathetic fibers in the wall of the carotid artery (see Chapter 10, Fig 10-4).

Figure 12-3 Herpes zoster ophthalmicus. This 63-year-old woman developed left-sided scalp pain and a rash in the V_1 distribution on the left side. (Courtesy of Rod Foroozan, MD.)



Herpes Zoster Ophthalmicus

When herpes zoster involves CN V dermatomes, pain may arise in the affected region days before a vesicular eruption appears (Fig 12-3). The pain is described as aching or burning. Occasionally, no vesicles are apparent (*zoster sine herpette*). Acutely, the pain may be exacerbated by concomitant iritis. The pain may persist long after resolution of the acute infection (*postherpetic neuralgia*), and it can be extremely discomforting and difficult to treat. Pregabalin, gabapentin, tricyclic antidepressants, and topical 5% lidocaine patches may be effective for some patients. Treatment with antiviral drugs during the acute phase may decrease the risk of severe postherpetic neuralgia. The zoster vaccine, offered to immunocompetent persons aged 60 years and older, significantly reduces the incidence of herpes zoster and markedly decreases the incidence and morbidity of postherpetic neuralgia. (See Chapter 7 in BCSC Section 9, *Uveitis and Ocular Inflammation*, for further discussion on herpes zoster.)

Oxman MN, Levin MJ, Johnson GR, et al; Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005; 352(22):2271–2284.

Neoplastic Processes

Facial numbness with or without pain suggests pathologic involvement of CN V, such as neoplastic processes that affect the nerve in the area of the cavernous sinus and the Meckel cave. Rapidly growing tumors, such as aggressive undifferentiated malignancies, may produce pain in a large percentage of patients. Facial cutaneous malignancy may be associated with *perineural invasion* and cause progressive pain, numbness, and multiple CN palsies. Patients should therefore be specifically questioned about prior facial malignancies. Orbital imaging may reveal enlargement of the inferior or superior orbital nerves; a biopsy of these nerves can confirm the diagnosis.

The Patient With Nonorganic Ophthalmic Disorders

Nonorganic ophthalmic disorders can occur in children or adults and are diagnosed after the clinician determines that there is no physiologic or organic basis for the patient's symptoms. A diagnosis of nonorganic vision loss is not a diagnosis of exclusion but rather an active diagnosis that requires confirmatory findings.

Malingering refers to the willful feigning or exaggeration of symptoms. Litigation involving monetary compensation or disability status is frequently an issue with these patients. Secondary psychological gain is often the underlying basis of *Münchhausen syndrome*, in which patients intentionally induce physical damage. *Hysteria* is a subconscious expression of nonorganic signs or symptoms; patients with hysteria are often unconcerned about their incapacitating symptoms (exhibiting “la belle indifférence”). The terms *functional*, *nonphysiologic*, and *nonorganic* are preferable when describing this disease spectrum. A substantial proportion of patients with actual organic disease may also exhibit superimposed nonorganic behavior. Patients with so-called nonorganic overlay may be very challenging; the clinician must ensure that the organic portion of disease is properly identified and treated (Table 13-1).

Table 13-1 Organic Disorders Frequently Misdiagnosed as Nonorganic Disorders

Big blind-spot syndrome, acute zonal occult outer retinopathy
Bilateral retrochiasmal disease (eg, occipital infarcts)
Chiasmal disease without optic atrophy (eg, craniopharyngioma)
Cone-rod dystrophy
Early keratoconus, irregular astigmatism
Early posterior subcapsular cataracts
Leber hereditary optic neuropathy
Maculopathy (eg, subtle central serous retinopathy, macular edema, epiretinal membrane)
Paraneoplastic retinopathy
Retinitis pigmentosa sine pigmento
Retrobulbar optic neuropathy
Stargardt disease

Adapted from Albert DM, Miller JW, eds. *Albert & Jakobiec's Principles & Practice of Ophthalmology*. 3rd ed. Philadelphia: Saunders/Elsevier; 2008:4019.

Clinical Profile

The first step in identifying a patient with a nonorganic disorder is to have a high index of suspicion when the patient's pattern of vision loss does not fit the common sequence of known diseases. For example, trivial external trauma to the eye should not cause long-term disabling vision loss. Potential secondary gain factors may become evident as the examiner records the patient's history. Some patients may be more focused on impending litigation or disability determination than on the diagnosis or treatment of their complaint.

"Everything counts" should be the clinician's guiding principle. Each piece of information about the patient, from the time the appointment is made through completion of the office visit, may help direct the examination. For example, patients wearing sunglasses to their appointments were found to be more likely to have nonorganic vision loss. The patient's general behavior and ocular capabilities should be observed throughout the examination. Can the patient successfully walk into the room and take a seat in a chair or shake the physician's silently outstretched hand? Does the patient appear to have difficulty with nonvisual tasks such as signing in at the front desk? Displaying empathy, employing active listening, and carefully recording the patient's story help the clinician to ensure that the doctor-patient relationship remains productive and nonconfrontational.

Suspicion should increase if the ophthalmic examination demonstrates a mismatch between objective and subjective findings. Examiners must be patient, persistent, and confident with the tests being used. The examiner can use *misdirection* to encourage a patient's belief that a particular eye or function being tested is part of a normal eye examination, when in reality the examiner may be working to confirm a nonorganic disorder by demonstrating a nonphysiologic response, improved visual acuity, visual fields, or ocular motility.

A diagnosis of a nonorganic component can be confirmed when the patient does something that should not be possible based on the stated symptoms. Some tests may yield results that suggest the patient is not cooperating but do not prove a nonorganic disorder. The examination must be tailored to the individual and the specific concerns.

Although the scope and economic impact of nonorganic ophthalmic disorders are difficult to measure, somatic manifestations of psychogenic origin may account for at least 10% of patient visits to family physicians. The cost to society from nonorganic ophthalmic disturbances is enormous.

Bengtzen R, Woodward M, Lynn MJ, Newman NJ, Biousse V. The "sunglasses sign" predicts nonorganic visual loss in neuro-ophthalmologic practice. *Neurology*. 2008;70(3):218–221.

Bose S. Nonorganic Visual Disorders. In: Albert DM, Miller JW, eds. *Albert & Jakobiec's Principles and Practice of Ophthalmology*. 3rd ed. Philadelphia: Saunders/Elsevier; 2008: 4017–4028.

Miller NR, Subramanian P, Patel VR, eds. Neuro-ophthalmologic manifestations of non-organic disease. In: *Walsh and Hoyt's Clinical Neuro-ophthalmology: The Essentials*. 3rd ed. Baltimore: Lippincott Williams & Wilkins; 2016:451–464.

Toldo I, Pinello L, Suppiej A, et al. Nonorganic (psychogenic) visual loss in children: a retrospective series. *J Neuroophthalmol*. 2010;30(1):26–30.

Examination Techniques

The clinician's main goals for the examination of patients with suspected nonorganic ophthalmic disorders are:

- exclude an organic cause by performing a thorough and complete history and examination
- distinguish organic findings from nonorganic findings
- meticulously test for positive clinical features that support the diagnosis

The examination is based on symptoms that may manifest in the following categories:

1. afferent visual pathway (visual acuity and visual field)
2. ocular motility and alignment
3. pupils and accommodation
4. eyelid position and function

Afferent Visual Pathway

Selection of the appropriate tests of the afferent visual pathway will depend on whether the dysfunction appears to be visual acuity loss (complete or partial, bilateral or monocular) or a visual field defect.

Bilateral no light perception

Several tests, visual and nonvisual, are used when a patient reports complete bilateral blindness (ie, no light perception). A patient's inability to perform nonvisual tasks may provide evidence of a nonorganic component to that patient's report of total blindness. Proprioceptive testing, such as failure to sign a paper or adequately perform a finger-to-nose test, in the absence of systemic neurologic diseases, should alert the clinician to problems (conscious or unconscious) with patient cooperation.

Finger-touching test In this test, the patient is asked to touch the fingertips of each hand together. A truly blind person can easily touch the fingertips together, because it requires proprioception, not vision (Fig 13-1). Therefore, a patient who claims to have no vision but cannot touch the fingertips of each hand together is responding in a nonphysiologic fashion.

Pupillary reaction The presence of normal pupillary reactions suggests that the anterior visual pathways are intact. However, it does not prove the loss is nonorganic; there could be involvement of the bilateral anterior visual pathways or the pathways posterior to the branching of axons to the pretectal nuclei (eg, lateral geniculate nucleus, optic radiations, or occipital cortex). An aversive light reaction by a patient who claims blindness establishes at least some level of afferent input.

Optokinetic nystagmus drum Perhaps the easiest test to perform is to slowly rotate an optokinetic nystagmus (OKN) drum in front of the patient. If the patient claims to see nothing but the patient's eyes move with the drum, a nonorganic component has been established.

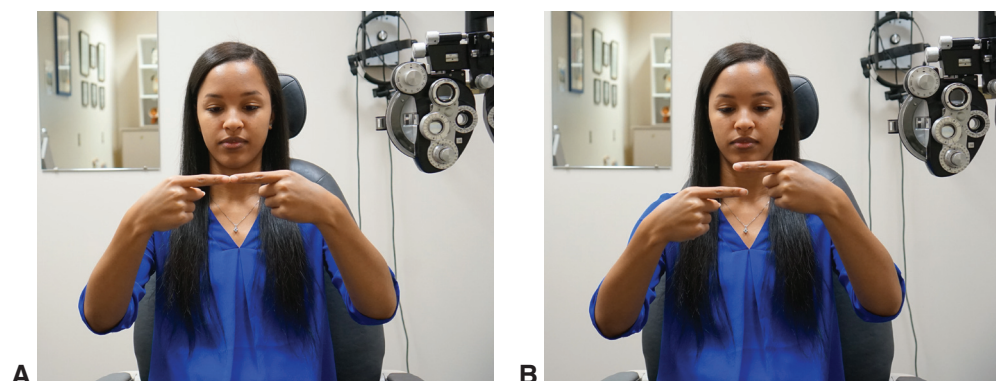


Figure 13-1 Finger-touching test. The patient is asked to touch the tips of the index finger of each hand together. **A**, A truly blind patient can easily perform this task. **B**, A patient with nonorganic visual loss may demonstrate the inability to touch the fingers together. (Courtesy of M. Tariq Bhatti, MD, and Mays A. El-Dairi, MD.)

It is possible for malingerers to purposely minimize or prevent the response by looking around or focusing past the drum.

Mirror test In this test, a large mirror is slowly rotated side to side in front of the patient. As in the drum test, if the patient claims to see nothing but the examiner notes eye movement with the mirror, then a subjective–objective mismatch has been documented.

Electrophysiologic testing Flash and pattern-reversal visual evoked potentials (VEPs) can play a role in assessing a possible nonorganic disorder. Although both false-positive and false-negative results are possible, the results can be used to confirm organic disease, for example a VEP with increased latency and decreased amplitude. Normal VEP results for a patient who reports severe monocular or binocular vision loss and who has normal clinical examination findings support a diagnosis of nonorganic disturbance of vision. An abnormal pattern-reversal visual evoked response in a patient who has normal findings on neuro-ophthalmic examination should not, by itself, lead to a diagnosis of an organic defect. A patient can use a variety of techniques (eg, inattention, lack of concentration, meditation, defocusing) to willfully suppress a visual evoked response (see the section “Visual evoked potential” in Chapter 3).

Monocular no light perception

All of the tests described for bilateral no light perception may be performed unilaterally. The clinician may also employ tests that involve ocular viewing confusion or tests that require binocularity.

Relative afferent pupillary defect In patients who claim complete vision loss in 1 eye only, the absence of a relative afferent pupillary defect (RAPD) substantially increases, but does not confirm, the likelihood of nonorganic visual loss when eye examination findings are normal (see Chapter 3).

Base-out prism test For this test, the clinician places a 4–6 prism diopters (Δ) prism base-out in front of 1 eye while the patient keeps both eyes open; normally, this procedure

elicits an inward shift of that eye (either as a conjugate saccade followed by a convergent movement of the opposite eye or by a convergent movement alone). Movement that occurs when the prism is placed over the eye with worse vision (“bad eye”) indicates vision in that eye.

Vertical prism dissociation test A 4 Δ prism is placed base-down in front of the eye with better vision (“good eye”) of a patient who reports monocular vision loss. If the subject has symmetric vision in both eyes, 2 images should be seen, 1 above the other. If the subject is able to see the letters only with the “good” eye, then only 1 image should be seen (Fig 13-2).

Golnik KC, Lee AG, Eggenberger ER. The monocular vertical prism dissociation test. *Am J Ophthalmol.* 2004;137(1):135–137.

Confusion tests For confusion tests to be successful, the patient must be unaware of which eye is actually being tested. Testing must appear to be simply a normal part of the examination. Any suspicion on the part of the patient will be detrimental to the test interpretation.

FOGGING TEST In this test, the clinician employs a trial frame with plus and minus cylinder lenses (6 diopters [D]), which have their axes aligned; these are placed in front of the patient’s “good” eye. The patient is asked to read the Snellen chart while one of the cylinder lenses is rotated. The rotation will severely blur vision as the two axes are rotated out of alignment. If the patient continues to read, he or she is doing so with the “bad” eye (Fig 13-3).

DUOCHROME TEST The examiner places duochrome (Worth 4-dot) glasses over the patient’s eyes, with the red lens over the “bad” eye. The red-green filter is then placed over the Snellen chart, presenting the letters simultaneously either on a green or a red background. The green lens will prevent the good eye from seeing the red background letters. If the red letters are read, the patient is reading with the “nonseeing” eye (Fig 13-4).

POLARIZED LENS TEST The patient wears the polarized lenses that are used in the stereoacuity test while reading a chart specially projected with corresponding polarized filters.

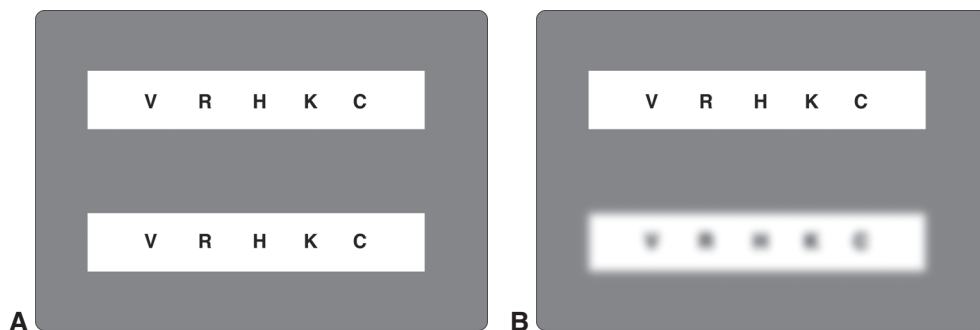


Figure 13-2 Monocular vertical prism dissociation test. **A**, With nonorganic vision loss, the patient will describe seeing 2 images, 1 over the other. **B**, True organic vision loss will render the patient unable to see the second image or to see only a very blurred second image. (Courtesy of Lanning Kline, MD.)

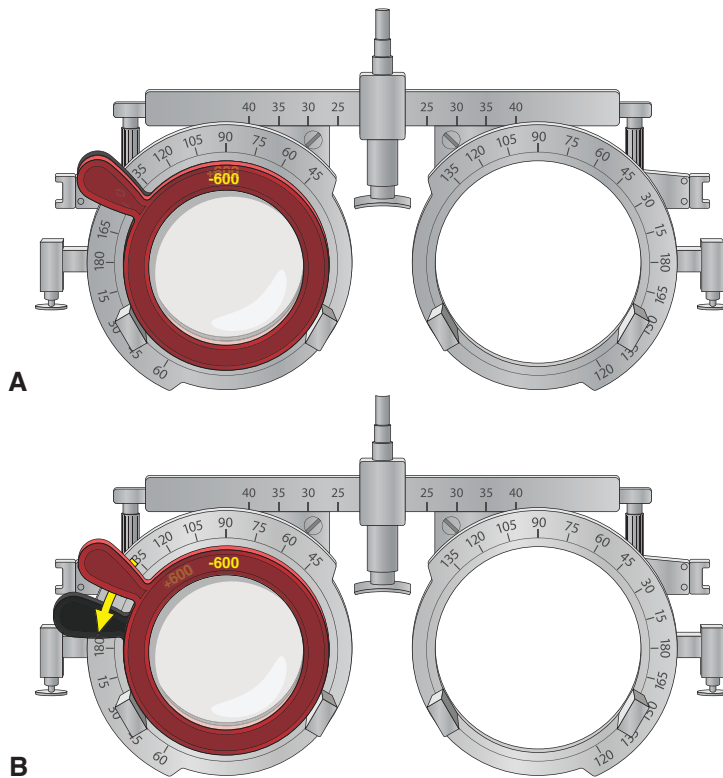


Figure 13-3 Fogging technique demonstrating the use of paired cylinders. **A**, A trial frame with +6D and -6D cylinder lenses are placed at parallel axes in front of the “good” eye. **B**, As the patient reads the Snellen chart, a small turn of the cylinder axis for 1 lens makes the axes no longer parallel and blurs the image seen by the “good” eye, so that the patient is now reading with the “bad” eye. (Illustration by Mark Miller.)



Figure 13-4 Duochrome test. **A**, A patient with nonorganic visual loss wears red-green glasses (red over the left eye) and views a duochrome chart, unknowingly reading both sides of the chart. **B**, A patient with organic visual loss of the left eye is unable to read the left side of the chart.

The clinician can ask the patient to read specific letters or lines to determine whether the patient is reading with the “bad” eye.

Stereopsis testing Stereopsis requires binocular vision. Patients may be tested for stereopsis with the standard stereoacuity test (using their appropriate near correction). Any evidence of stereopsis demonstrates that vision is present in the “bad” eye. It should be noted that patients with vision in only 1 eye may be able to detect asymmetries in the first several circles on the basis of monocular clues. However, if the circle is “standing out from the page,” the patient has binocularity.

Monocular reduced vision

Patients who report symptoms of reduced vision are more challenging. The clinician must convincingly demonstrate that the patient has better visual acuity than initially claimed. Many of the tests described for patients with binocular or monocular no light perception can also be used for patients with monocular (and binocular) reduced vision.

Confusion tests The confusion tests described in the section “Monocular no light perception” are useful if the patient reports substantial reduction in visual acuity in 1 eye. The fogging test, duochrome test, and polarized lens test may help the clinician obtain a quantitative visual acuity measurement if the patient is cooperative enough to continue reading. Unlike the assessment of a patient who claims monocular blindness, in this case, simply demonstrating that the patient can read is not sufficient; the clinician must determine the actual visual acuity.

Stereopsis testing As previously stated, the presence of stereopsis indicates that the patient has at least some vision in both eyes. Although attempts have been made to equate visual acuity and quantitative stereopsis, this relationship suggests, but does not establish, nonorganic vision loss (Table 13-2).

Table 13-2 Comparison of Visual Acuity to Stereopsis

Titmus Score in Wirt Circles (Stereoacuity in arc seconds)	95% Prediction Interval Snellen VA	99% Prediction Interval Snellen VA
9 (40)	20/40	20/79
8 (50)	20/45	20/95
7 (60)	20/50	20/120
6 (80)	20/62	20/180
5 (100)	20/76	20/270
4 (140)	20/110	20/570
3 (200)	20/180	20/1800
2 (400)	20/690	20/39000
1 (800)	20/5300	20/7600000

How to interpret Table 13-2: A patient who demonstrates visual acuity (VA) of 20/400 in the eye with poorer vision and scores 7 circles (60 arc seconds) would be expected to have visual acuity in the eye with poorer vision no worse than 20/50 with 95% prediction interval and no worse than 20/120 with 99% prediction interval.

Adapted from Sitko KR, Peragallo JH, Bidot S, Biousse V, Newman NJ, Bruce BB. Pitfalls in the use of stereoacuity in the diagnosis of nonorganic visual loss. *Ophthalmology*. 2016;123(1):198–202.

Binocular reduced vision

Binocular reduced vision is the most difficult symptom to address in patients with non-organic vision loss. Proving a nonorganic disorder requires time and patience from the examiner to induce the patient to admit to seeing better than initially claimed.

Bottom-up acuity This examination begins with a visual acuity determination on the smallest line on the Snellen chart (20/10). If the patient cannot see these letters, the examiner announces the use of a “larger line” and then switches to the 20/15 line and several different 20/20 lines. The examiner continually expresses disbelief that such “large” letters cannot be identified. If the patient still denies being able to read the letters, he or she is asked to determine the number of characters present and whether the characters are round, square, and so on. The examiner might suggest that the characters are letters and that the first one is easier to identify than the others. By the time the “very large letters” (ie, 20/50) are reached, the patient often can read optotypes much smaller than initially identified.

Alternately, small ($\frac{1}{8}$ D) plus and minus lenses or small cylinders are added and subtracted while the patient is asked how many letters are visible and what shape they are. It is sometimes possible to gradually improve the best-recorded visual acuity with this method.

“Visual aids” The examiner can have the patient wear trial frames with 4 lenses equaling the correct prescription but suggest that they are special magnifying lenses that might enable improved vision. The potential acuity meter can also be presented as a means of “bypassing the visual block.” Improvement in either case suggests a nonorganic component.

Use of alternative charts Patients may be persuaded to see substantially better by a switch in optotypes. For example, a patient who refuses to read type smaller than 20/200 using standard optotypes might read much better from a tumbling E chart or a chart with numbers.

Specialty charts Specialty charts with the top line in 50 optotype instead of 400 optotype are available. Patients who say they can read only the “top line” immediately improve their resolution by 4 lines. Alternatively, the standard chart may be moved farther away.

Visual field defect

Although less common than visual acuity loss, patients do occasionally report difficulty seeing on 1 side. The problem may be binocular but is more commonly monocular with nonspecific constrictions.

Automated perimetry testing In general, this type of testing is not helpful in distinguishing organic from nonorganic visual field loss. The machines are quite easy to fool; if motivated, an observer can reproduce homonymous defects, altitudinal defects, or even arcuate and central scotomata. Nonetheless, central scotomata are extremely rare in nonorganic vision loss and warrant further evaluation. There are no characteristic changes in automated perimetry testing results that would confirm the suspicion of a nonorganic deficit. However, one unusual situation in which automated perimetry testing might be useful would be for a patient with a monocular defect that appears to respect the vertical midline. If repeating

the field testing with both eyes open produces a similar, or even incomplete or “missing-half,” defect, then a nonorganic component is present (Fig 13-5).

Frisen L. Identification of functional visual field loss by automated static perimetry. *Acta Ophthalmol.* 2014;92(8):805–809.

Sitko KR, Peragallo JH, Bidot S, Biousse V, Newman NJ, Bruce BB. Pitfalls in the use of stereo-acuity in the diagnosis of nonorganic visual loss. *Ophthalmology.* 2016;123(1):198–202.

Confrontation testing This test is useful in the case of a dense visual field defect. The area where the patient “can’t see” is carefully identified. Later, the patient is tested for “motility.” As part of this examination, stimuli are placed in various areas of the patient’s peripheral

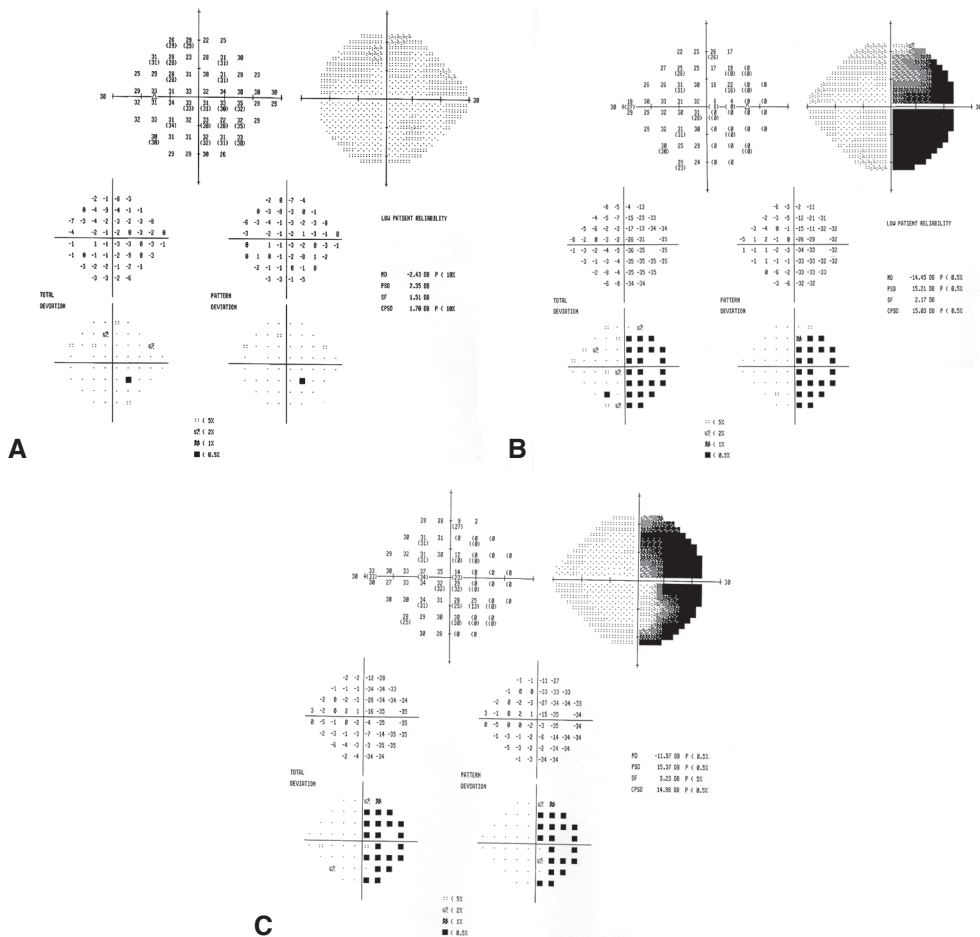


Figure 13-5 “Missing-half” field defect. A 33-year-old man complained of decreased vision temporally in the right eye after being in a motor vehicle accident. Automated perimetry testing demonstrates a normal field in the left eye (A) and a temporal defect in the right eye (B). Visual field testing performed with both eyes open (C) demonstrates persistence of the visual field defect, indicating a nonorganic basis for the visual complaint. (Courtesy of Karl C. Golnik, MD.)

field, including those areas where the patient “couldn’t see.” Accurate saccades to these nonauditory targets indicate an intact visual field.

In some cases, confrontation testing (“silent visual fields”) might initially appear to confirm a dense visual field defect. The patient is subsequently asked to count fingers in the “nonseeing” field and is instructed to report “none” when no fingers are seen. As the test progresses, the examiner begins showing fingers without saying anything. A response of “none” each time the fingers are put up confirms vision in that area.

Kinetic perimetry testing In manual kinetic perimetry (Goldmann) testing, the visual field is tested continuously in a clockwise or counterclockwise direction starting with the I4e stimulus. A common nonorganic response shows a spiraling isopter getting closer and closer to fixation as testing continues. As larger stimuli (III4e and V4e) are employed, there is often further constriction, resulting in overlapping isopters (Fig 13-6). The latter can also be detected with automated kinetic perimetry. It is important to make sure there is no step across the vertical or nasal horizontal midline; a step across the midline may indicate that at least some physiologic component is present in the field abnormality.

Tangent screen testing In tangent screen testing, the patient is tested with a 9-mm white stimulus at 1 m. The areas of patient response are marked and the patient is moved back to 2 m. The test is then repeated using an 18-mm white stimulus. The field should expand to twice the original size. Failure to expand (tubular or gun-barrel field) is nonphysiologic and indicates a nonorganic component to the field constriction (Fig 13-7).

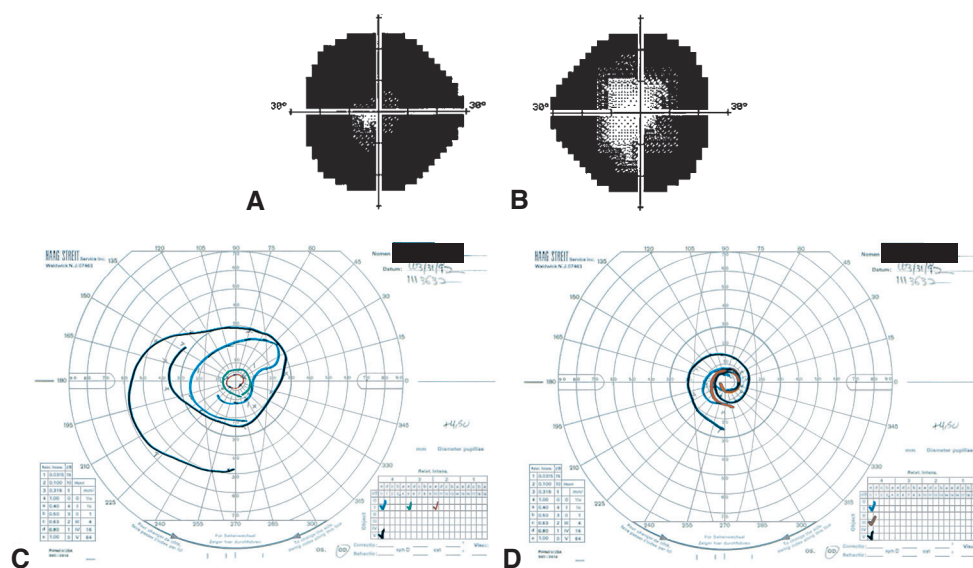


Figure 13-6 A 59-year-old woman complained of 1 year of headaches. **A, B**, Automated static perimetry using a V-sized test object demonstrated severe constriction. **C, D**, Subsequent kinetic perimetry visual field testing revealed crossing and spiraling isopters, indicating nonphysiologic constriction of the visual fields. (Courtesy of Steven A. Newman, MD.)

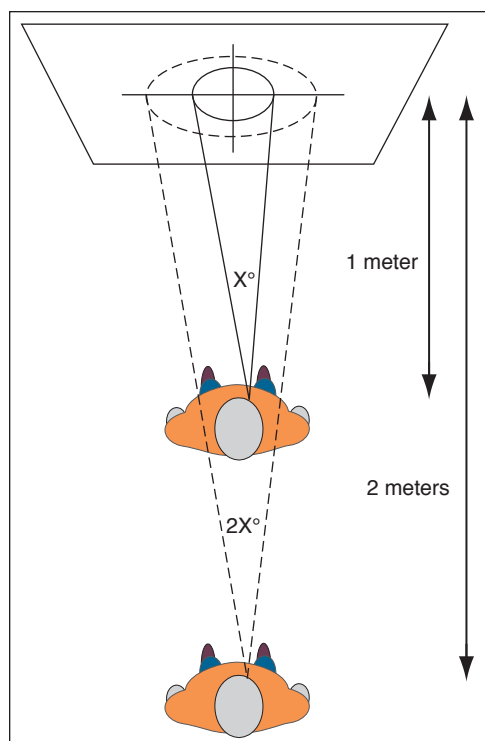


Figure 13-7 The tangent visual field test at 1 and 2 meters (m). The visual field normally expands on increasing the testing distance from 1 to 2 m. This is due to the increase in the visual angle from X° to $2X^\circ$. In a patient with nonorganic vision loss, the normal expansion of the visual field is absent and remains contracted despite the increase in testing distance. (Based on an illustration by Swaraj Bose, MD.)

Ocular Motility and Alignment

Voluntary flutter ("nystagmus")

Voluntary flutter, which is sometimes misdiagnosed as nystagmus, is characterized by irregular, brief bursts of rapid-frequency and low-amplitude eye movements with no slow phase (see Chapter 9).

Gaze palsy

Patients may report an inability to move the eyes horizontally or vertically. Such claimed gaze palsies may be overcome by a variety of maneuvers or tests, such as including those in oculocephalic reflex (doll's head phenomenon), OKN drum, mirror tracking, and inner ear caloric stimulation.

Spasm of the near reflex

Spasm of the near reflex is characterized by episodes of intermittent convergence, increased accommodation, and miosis. Patients generally report diplopia and, at times, micropsia. The degree of convergence is variable, ranging from a large esotropia to only 1 eye turning in. This syndrome may be mistaken for unilateral or bilateral cranial nerve (CN) VI palsies, divergence insufficiency, horizontal gaze paresis, or ocular myasthenia gravis. Variability of the eye movements, miosis with convergent eye movements, and lack of other neuro-ophthalmic abnormalities are clues that can help the examiner reach the

correct diagnosis. Further, when ductions are examined with 1 eye occluded or with oculocephalic testing, both eyes demonstrate full abduction, and the miosis observed with the eyes in an esotropic position immediately resolves. Although spasm of the near reflex is almost always observed in patients with nonorganic disturbances, it has also been associated with Arnold-Chiari type I malformation, posterior fossa tumors, pituitary tumors, and head trauma.

Pupils and Accommodation

Fixed, dilated pupil

Few patients provoke more concern regarding a potentially life-threatening neurologic condition than those with headaches and a fixed, dilated pupil. The differential diagnosis can be narrowed to pharmacologic blockade, CN III palsy, and Adie tonic pupil. *Pharmacologic blockade* may occur because of inadvertent or purposeful application of mydriatic or cycloplegic eyedrops; it may also occur after touching the eyes with fingers contaminated through use of a scopolamine patch or touching certain plants that contain parasympatholytic chemicals.

The pilocarpine test distinguishes parasympathetic denervation from pharmacologic blockade. In pharmacologic blockade, 1% pilocarpine cannot overcome the receptor blockade, and the pupil remains large. Dilute pilocarpine will constrict a dilated pupil in a majority of patients with either a CN III palsy or Adie tonic pupil. See Chapter 10 for further discussion of pupillary abnormalities.

Changes in pupil size

Widely dilated pupils may be observed in young patients, most likely caused by increased levels of circulating catecholamines. A few patients are able to voluntarily dilate both pupils. Intermittent miosis occurs in spasm of the near reflex (discussed earlier), accompanied by esotropia and accommodation.

Changes in accommodation

Weakness or paralysis of accommodation sometimes occurs, primarily in children and young adults. Such patients may complain of an inability to read clearly even in the presence of an appropriate plus lens. If a patient with normal distance vision fails to read despite appropriate near-vision correction, a nonorganic condition is possible.

Spasm of accommodation can be observed with spasm of the near reflex. Patients may report blurred distance vision and often can produce 8–10 D of myopia. Refraction with and without cycloplegia during the period of spasm establishes the presence of the induced myopia.

Eyelid Position and Function

Ptosis

Eyelid “droop” from nonphysiologic causes can usually be distinguished by the position of the brow. In a patient with true ptosis, the brow is usually elevated as the patient tries to widen the palpebral fissure. With orbicularis overactivity, the brow is lowered.

Patients who feign ptosis generally cannot simultaneously elevate the eye and maintain a drooping eyelid. Thus, with upward gaze, the ptosis will “resolve.” Often the patient will realize this and not cooperate. In such cases, the examiner can use his or her thumb to manually elevate the ptotic eyelid and the patient will then look upward. The examiner’s thumb is then slowly moved away. If the ptosis returns, the condition may well have an organic basis, but if it “resolves,” then it is nonorganic.

Blepharospasm

Nonorganic blepharospasm may be unilateral or bilateral and typically occurs in children or young adults. It may be triggered by an emotionally traumatic event and may cause nonorganic ptosis. Pressure over the supraorbital notch is often useful in raising the eyelids.

Management of the Patient With Nonorganic Ophthalmic Disorders

After taking a detailed history and performing a thorough examination, the clinician needs to clearly document that no organic damage to the visual system was detected. In addition, the clinician should highlight any specific findings from the clinical examination and tests that confirm the inconsistencies and suggest a nonorganic etiology.

Patients with nonorganic visual disorders are best managed with understanding and encouragement. Confrontation is seldom beneficial, and it is prudent to allow patients a graceful way out by reassuring them that their disorder, while unlikely to reflect a serious condition, is a problem that will resolve over time. Often, the symptoms will clear after 1 or 2 follow-up visits, and patients should be reassured of an “excellent prognosis.” This approach is usually more effective with children than adults. Children may be further encouraged through the prescription of “eye rest”—for example, by limiting the use of electronic technology and entertainment devices.

In patients with combined organic and nonorganic (nonorganic overlay) complaints, it is best to manage the organic problem and attempt to downplay the nonorganic portion. In some cases, consultation with a psychiatrist or psychologist may be warranted for an underlying psychological illness. Finally, it is always important to monitor a patient with what initially appears to be a nonorganic visual disturbance. Occasionally, an organic disorder becomes apparent later and can be managed appropriately.

Leavitt JA. Diagnosis and management of functional visual deficits. *Curr Treat Options Neurol.* 2006;8(1):45–51.

Scott JA, Egan RA. Prevalence of organic neuro-ophthalmologic disease in patients with functional visual loss. *Am J Ophthalmol.* 2003;135(5):670–675.

Selected Systemic Conditions With Neuro-Ophthalmic Signs



This chapter includes a related video, which can be accessed by scanning the QR code provided in the text or going to www.aaao.org/bcscvideo_section05.

Certain neurologic and medical disorders are encountered commonly enough within the context of an ophthalmic clinical practice and affect vision with such frequency that they deserve separate emphasis. Although the following discussion is not comprehensive, it is intended to cover many aspects of diseases with which ophthalmologists should be familiar.

Immunologic Disorders

Of the variety of immune system–mediated disorders that produce neuro-ophthalmic signs and symptoms, giant cell arteritis, multiple sclerosis, myasthenia gravis, thyroid eye disease, and sarcoidosis are the most common.

Giant Cell Arteritis

Giant cell arteritis (GCA), or *temporal arteritis*, is a systemic inflammatory granulomatous vasculitis that involves large- and medium-sized arteries and affects mainly white people over 50 years of age almost exclusively. The incidence of the disease increases with age; it is 20 times more common in the ninth decade than the sixth decade. GCA is 2–4 times more likely to affect women than men, and it is more common in people of Northern European and Scandinavian descent. Early diagnosis and treatment of GCA can limit or prevent permanent vision loss.

Clinical presentation of giant cell arteritis

Systemic symptoms of GCA include headache and tenderness of the temporal artery or scalp. Jaw or tongue claudication (a cramping pain that develops while chewing or talking) is the symptom most specific for the disorder; other symptoms include malaise, anorexia and weight loss, fever, new neck pain, ear pain, and joint and muscle pain. Systemic sequelae can include cerebrovascular ischemia, myocardial infarction, and aortic aneurysm or dissection.

Visual symptoms may include diplopia or transient or permanent vision loss. The most common cause of vision loss is *arteritic anterior ischemic optic neuropathy (AAION)*

(see Chapter 4, Fig 4-10), but central retinal artery occlusion (CRAO), cilioretinal artery occlusion, posterior ischemic optic neuropathy, choroidal infarction, ocular ischemic syndrome, and orbital ischemia also occur. Ischemia of the ocular motor cranial nerves (CNs), extraocular muscles, or brainstem can result in transient or constant diplopia.

Diagnosis of giant cell arteritis

When evaluating patients over age 50 with the visual symptoms just described, a high level of suspicion of GCA is paramount. Diagnostic evaluation begins with laboratory tests of the erythrocyte sedimentation rate (ESR), complete blood count (CBC), and C-reactive protein (CRP). Most cases of GCA show marked elevation of the Westergren ESR (mean 70 mm/hr; often >100 mm/hr), but the level may be normal in up to 16% of cases. The ESR rises with anemia and with increasing age; levels above the laboratory's listed upper limit of normal are common in patients older than 70 years without arteritis. A more accurate estimate of the upper normal value can be obtained by using these formulas: $[\text{age}]/2$ (*men*) or $[\text{age} + 10]/2$ (*women*). Measurement of CRP level, which may be more specific and less affected by increasing age and anemia, may increase diagnostic accuracy and is typically obtained in conjunction with the ESR. Thrombocytosis (increased platelet count) may suggest active disease. A normochromic normocytic anemia may be present.

Whenever clinical suspicion or laboratory studies suggest the possibility of GCA, temporal artery biopsy (TAB) should be performed, ideally at a site of localized tenderness and/or on the side of the vision loss (see BCSC Section 4, *Ophthalmic Pathology and Intraocular Tumors*). The TAB needs to be done as soon as possible, ideally within 2 weeks, but in some cases remains positive for months after initiation of therapy. A unilateral TAB can be falsely negative in approximately 3%–15% of cases. Factors that may produce a false-negative unilateral TAB include discontinuous arterial involvement (“skip areas”), missed lesions, or inadequate sections (under 2 cm long). If the index of suspicion remains high, a contralateral TAB is typically performed. Other imaging strategies such as color Doppler ultrasonography, positron emission tomography (PET), and magnetic resonance imaging (MRI) may provide additional useful diagnostic clues; however, TAB remains the gold standard for GCA diagnosis.

El-Dairi MA, Chang L, Proia AD, Cummings TJ, Stinnett SS, Bhatti MT. Diagnostic algorithm for patients with suspected giant cell arteritis. *J Neuroophthalmol*. 2015;35(3):246–253.

Treatment of giant cell arteritis

Corticosteroids are the mainstay of treatment of GCA; they should be initiated immediately when GCA is suspected. Approximately 50% of patients with GCA and vision loss in 1 eye will lose vision in the opposite eye within 7 days if the GCA is left untreated. Intravenous methylprednisolone (1 g/day for the first 3–5 days) is often recommended when vision loss is present. For patients with suspected GCA but without loss of vision, oral prednisone 60–100 mg/day may be sufficient. Treatment is also required for patients with severe, bilateral vision loss because GCA is a systemic disease. The clinical response to corticosteroids is often dramatic; symptoms may be reduced within days. The corticosteroids are generally tapered slowly, depending on response, and patients typically continue therapy for at least 1–2 years, sometimes longer. Patients undergoing long-term corticosteroid therapy should be monitored and treated as necessary for osteopenia and

osteoporosis as well as prophylaxis of gastrointestinal effects; it is recommended that these patients be comanaged with a rheumatologist or internist. Corticosteroid treatment does not generally improve vision, but it may prevent new ischemic events from occurring. The risk of recurrent or contralateral optic nerve involvement during withdrawal from corticosteroid treatment has been reported at 7%; thus, as mentioned, tapering must be done slowly and carefully. Patients must also be monitored for thoracic and aortic aneurysms, which are associated with GCA. Additionally, these patients are at increased risk of cerebrovascular and cardiovascular ischemia; thus, low-dose aspirin administration should be considered.

Multiple Sclerosis

Multiple sclerosis (MS), an inflammatory and neurodegenerative disorder of the central nervous system (CNS), causes progressive neurologic disability over time. Patients with MS frequently have visual symptoms, and the ophthalmologist is often the first physician consulted. Familiarity with both the ocular and neurologic consequences of MS is important for guiding the ophthalmologist to the appropriate diagnosis.

Epidemiology and genetics of multiple sclerosis

The prevalence of MS varies widely. It is more common in whites and in individuals living in latitudes greater than 40 degrees from the equator and is 2–3 times more likely to affect women than men. MS is relatively uncommon in children younger than 10 years; the incidence is highest among young adults (25–40 years). However, onset even after the age of 50 years is not rare.

The cause of MS remains unknown. Vitamin D deficiency is a risk factor for MS. The risk of MS is also significantly increased in first-degree relatives of patients with the disease. Although there is a strong association with the HLA-DRB1 antigen, the genetic associations are multifactorial.

Course and prognosis of multiple sclerosis

Most patients with MS (85%) initially experience a relapsing-remitting clinical course with episodes of neurologic dysfunction that are separated by intervals of months or years. However, MRI studies have revealed that pathologic disease burden in the CNS accumulates even in the absence of clinical activity. Within 10 years, approximately 50% of patients with relapsing-remitting disease exhibit a slow, apparently continuous deterioration in neurologic status (secondary progressive form). In approximately 15% of patients, the disease progresses inexorably from onset with no recognizable attacks (primary progressive form). Near total disability and, in rare instances, death within 1–2 years of onset may result after a fulminant course. In contrast, about 5%–10% of patients experience a relatively benign course without serious disability or life span reduction.

Pathology in multiple sclerosis

Although MS is classically considered a demyelinating disease, axonal damage does occur early and is an integral part of the disease process. This axonal loss manifests as “black holes” on T1-weighted MRI sequences (Fig 14-1). Myelin destruction is associated with local perivascular mononuclear cell infiltration, myelin removal by macrophages, and

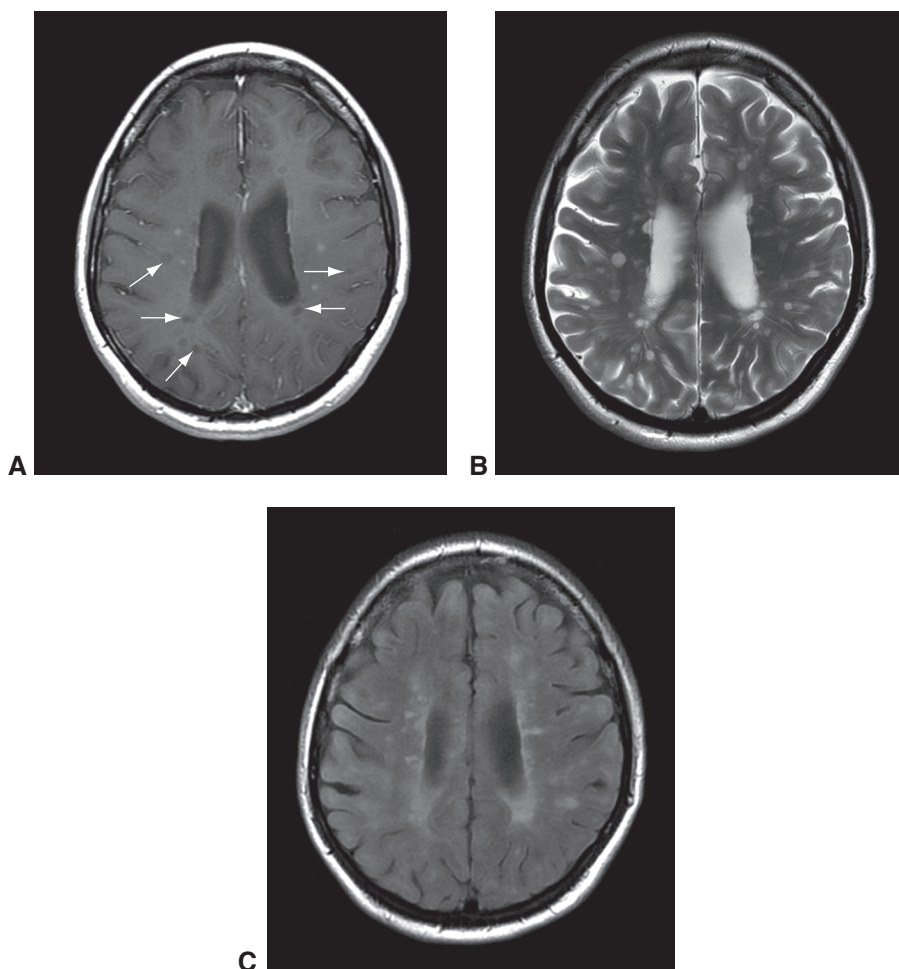


Figure 14-1 Axial magnetic resonance imaging (MRI) scans of a patient with multiple sclerosis (MS) show demyelinating plaques. **A**, T1-weighted, postgadolinium MRI scan demonstrates enhancing white matter lesions bilaterally, as well as “black holes” (arrows). **B**, T2-weighted MRI scan shows periventricular, multifocal, hyperintense white matter lesions consistent with demyelination. **C**, A fluid-attenuated inversion recovery (FLAIR) scan confirms periventricular white matter lesions. (Reprinted with permission from Slack: Lee AG, Brazis PW, Kline LB. Curbside Consultation in Neuro-Ophthalmology: 49 Clinical Questions. Thorofare, NJ: Slack, 2009.)

astrocytic proliferation with production of glial fibrils. The term *multiple sclerosis* stems from the presence of these numerous gliotic (sclerotic) plaque lesions. Plaques are often situated in the white matter at the ventricular margins, the optic nerves and chiasm, the corpus callosum, and the spinal cord and throughout the brainstem and cerebellar peduncles.

Criste G, Trapp B, Dutta R. Axonal loss in multiple sclerosis: causes and mechanisms. *Handb Clin Neurol*. 2014;122:101–113.

Clinical presentation of multiple sclerosis

The diagnosis of MS is made by identifying neurologic symptoms and signs that occur over time and that affect different areas of the CNS. Ocular symptomatology is commonly

part of the clinical picture of MS, and various ocular complications are discussed in the following sections. Nonocular signs and symptoms attributable to MS may precede, follow, or coincide with the ocular signs. Initially, many symptoms of MS are so transient or benign that the patient may fail to remember previous episodes. Typically, significant episodes last for weeks or months. The physician should ask specifically about transient diplopia, ataxia, vertigo, patchy paresthesias, bladder or bowel dysfunction, and extremity weakness. Fatigue and depression are common and may precede the onset of focal neurologic deficits. Symptoms of early MS are often so evanescent and unaccompanied by objective neurologic findings that they may be ignored.

The cerebellum, brainstem, and spinal cord may be involved individually or simultaneously, thus producing single or multiple symptoms. Some of the more common *non-ocular* symptoms include:

- *cerebellar dysfunction*: ataxia, dysarthria, intention tremor, truncal or head titubation, or dysmetria (sometimes described by the patient as poor depth perception)
- *mental changes*: emotional instability, depression, irritability, or fatigue; later in the course, cognitive dysfunction
- *motor symptoms*: extremity weakness, facial weakness, hemiparesis, or paraplegia
- *sensory symptoms*: paresthesias of face or body (especially in a bandlike distribution around the trunk), Lhermitte sign (an electric shock–like sensation in the limbs and trunk that is produced by neck flexion), or pain (occasionally, trigeminal neuralgia)
- *sphincter disturbances*: frequency, urgency, hesitancy, or incontinence; urinary retention that leads to urinary tract infection

Optic neuritis in multiple sclerosis

The clinical signs and symptoms of optic neuritis are discussed in Chapter 4. Even after recovering from vision loss brought on by demyelinating optic neuritis, patients may experience transient deterioration of vision during exercise or with small elevations in body temperature (Uhthoff phenomenon). Some patients with optic neuritis report phosphenes (bright flashes of light) with movement of the affected eye or photisms (light induced by noise, smell, taste, or touch). Importantly, 25% of patients have optic neuritis as a presenting symptom of MS, and their first evaluation will be performed by an ophthalmologist. Symptoms of optic neuritis occur at some point in 75% of patients, and evidence of optic nerve involvement as demonstrated by an abnormal visual evoked response appears in 90% of patients with MS. Furthermore, autopsy studies show anterior visual pathway demyelination in virtually all patients with clinically definite MS. There is increasing interest in the use of optical coherence tomography (OCT) to measure the retinal nerve fiber layer and retinal ganglion cell layer in MS as a marker for neuronal damage.

After an episode of optic neuritis, many patients want to know their risk of MS. The 15-year follow-up of the Optic Neuritis Treatment Trial (ONTT) showed that the strongest predictive factor in determining the likelihood that MS would develop was the presence or absence of abnormalities on MRI scan of the brain obtained at study entry during an episode of optic neuritis. Overall, clinically definite MS developed in 50% of ONTT patients in 15 years. However, the probability of developing clinically definite MS based on MRI scan appearance ranged from 25% for patients with no lesions on the brain MRI to 72% for patients with 1 or more lesions. Cerebrospinal fluid (CSF) analysis in a subgroup of

ONTT patients showed that oligoclonal banding had predictive value for the development of MS, but only in patients with a normal MRI scan at study entry. Patients with a history of prior optic neuritis and nonspecific neurologic symptoms were at higher risk of MS.

Costello FE, Klistorner A, Kardon R. Optical coherence tomography in the diagnosis and management of optic neuritis and multiple sclerosis. *Ophthalmic Surg Lasers Imaging*. 2011;42(Suppl):S28–S40.

Optic Neuritis Study Group. Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up. *Arch Neurol*. 2008;65(6):727–732.

Funduscopy abnormalities in multiple sclerosis

Retinal nerve fiber layer defects are discussed in Chapter 3. Uveitis is 10 times more common in MS patients than in the general population. Depending on the study, uveitis frequency in patients with MS varies widely, occurring in 0.4%–28.5% of patients. Ocular inflammation may develop concurrent with, prior to, or after the development of neurologic signs and symptoms. MS-related uveitis generally presents as intermediate uveitis (including pars planitis), and common findings include mild vitritis with periphlebitis. See BCSC Section 9, *Uveitis and Ocular Inflammation* for a more extensive review of MS-related uveitis.

Messenger W, Hildebrandt L, Mackensen F, Suhler E, Becker M, Rosenbaum JT. Characterization of uveitis in association with multiple sclerosis. *Br J Ophthalmol*. 2015;99(2):205–209.

Chiasmal and retrochiasmal abnormalities in multiple sclerosis

The white matter within the optic chiasm, optic tracts, and visual radiations is frequently involved pathologically in MS lesions. Lesions in these areas follow a recovery pattern similar to that of optic neuritis. Chiasmal or retrochiasmal visual field defects were observed in 13.2% of patients in the ONTT after 1 year of follow-up (see Chapter 4, Fig 4-29). Progressive multifocal leukoencephalopathy (PML) should be considered when a patient with MS using natalizumab presents with homonymous visual field defects (see Table 14-1 and the section Progressive Multifocal Leukoencephalopathy later in this chapter).

Ocular motility disturbances in multiple sclerosis

Diplopia is a frequent MS symptom. Motility abnormalities resulting from MS are typically localized to the supranuclear, nuclear, and fascicular portions of the ocular motor system. Internuclear ophthalmoplegia, especially when bilateral, may present with exotropia in primary position and bilaterally impaired adduction (ie, wall-eyed, bilateral internuclear ophthalmoplegia, or WEBINO; see Chapter 7, Fig 7-5); it is highly suggestive of MS in someone under age 50 years. Other signs include complete or partial paralysis of horizontal or vertical gaze or a skew deviation (vertical misalignment not attributable to single CN or muscle dysfunction). Although uncommon, MS should be considered in a young adult with an isolated ocular motor CN palsy and no history of trauma. Because ocular motor palsies most likely reflect fascicular involvement, they are frequently accompanied by other brainstem findings. CN VI involvement is most commonly reported, but CN III or CN IV paresis has also been described.

Nystagmus is frequently present in MS. It may be horizontal, rotary, or vertical, and both pendular and jerk types may occur. Concomitant vertical and horizontal nystagmus occurring out of phase produces circular or elliptical eye movements that are highly suggestive of MS. Common cerebellar eye findings include rebound nystagmus, fixation instability (macrosaccadic oscillations), saccadic dysmetria, and abnormal pursuit movements. Occasionally, MS lesions produce dorsal midbrain (Parinaud) syndrome. Patients with eye movement abnormalities typically report symptoms, including diplopia, blurred vision, or oscillopsia. See Chapters 7, 8, and 9 for further discussion on ocular motility disorders.

Diagnosis of multiple sclerosis

MS is diagnosed using the modified McDonald criteria, which are based on the combination of clinical history and presentation, along with neuroradiologic imaging, with or without CSF abnormality or an abnormal visual evoked response. Even an insidious neurologic progression suggestive of MS can lead to a definite diagnosis if appropriate paraclinical abnormalities are present. However, in the absence of other clinical or laboratory manifestations, recurrent optic neuritis is not sufficient for diagnosing MS.

Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald Criteria. *Ann Neurol*. 2011;69(2):292–302.

Laboratory evaluation of multiple sclerosis No test unequivocally establishes the presence of MS, which remains a *clinical* diagnosis. The CSF in patients with definite MS is abnormal in more than 90% of cases. The most common abnormalities are elevation of immunoglobulin G (IgG) level, elevation of the IgG/albumin index, and the presence of oligoclonal IgG bands (in CSF but not in serum). None of these findings, however, is specific for MS.

Neuroimaging in multiple sclerosis The neuroimaging study of choice for the diagnosis and management of MS is an MRI scan with *fluid-attenuated inversion recovery (FLAIR)* sequencing and gadolinium-DTPA (diethylenetriaminepentaacetic acid) infusion. The MRI scan is particularly sensitive for the identification of white matter plaques in the CNS, and it is far superior to CT scan for showing the posterior fossa and spinal cord (see Fig 14-1; see also Chapter 2, Fig 2-9, and Chapter 4, Fig 4-8). The MRI scan shows multiple lesions in 85%–95% of patients with clinically definite MS and in 66%–76% of patients with suspected MS. Although the abnormalities apparent on MRI scan are not specific for MS, multifocal lesions that are periventricular and ovoid are most consistent with the condition. The lesions observed with MRI fluctuate over time. Active lesions will enhance with gadolinium-DTPA administration. Hypointense regions on postcontrast T1-weighted scans (black holes) are also a marker of progressive disease. Lesions in the optic nerves of patients with symptomatic optic neuritis are best visualized on MRI scan with fat-suppression techniques and gadolinium-DTPA infusion (see Fig 4-8C).

Treatment of multiple sclerosis

There is no cure for MS; however, several therapies slow the disease and help alleviate specific symptoms. As in the management of optic neuritis, intravenous high-dose

corticosteroids are often used to treat acute exacerbations of MS. Although vitamin D deficiency is routinely corrected in newly diagnosed MS patients or in patients at risk of MS, the benefit of such therapy remains unproven.

Disease-modifying therapy (DMT) is typically recommended for long-term treatment of MS. Several studies, including CHAMPS (Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study), ETOMS (Early Treatment of Multiple Sclerosis), BENEFIT (Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment), and PreCISe (Early Glatiramer Acetate Treatment in Delaying Conversion to Clinically Definite Multiple Sclerosis in Subjects Presenting with a Clinically Isolated Syndrome), have demonstrated the benefits of early DMT initiation in subjects with clinically isolated syndrome (CIS) at risk of developing MS. There are several United States Food and Drug Administration (FDA)–approved disease-modifying drugs currently available for relapsing forms of MS (Table 14-1). These drugs, which should be used with caution, are often prescribed by physicians experienced in MS therapy. Novel drugs and combinations of immunomodulating therapies are being investigated.

Macular edema has been reported in 0.5% of patients treated with fingolimod, a once-daily oral medication approved for the treatment of relapsing MS. This ophthalmic complication, also known as FAME (fingolimod-associated macular edema), is more common in patients with diabetes and uveitis and is more likely to develop within 4 months of treatment initiation. The macular edema typically resolves upon cessation of fingolimod therapy. Figure 14-2 lists the screening protocol for FAME.

Eckstein C, Bhatti MT. Currently approved and emerging oral therapies in multiple sclerosis: an update for the ophthalmologist. *Surv Ophthalmol.* 2016;61(3):318–332.

Jain N, Bhatti MT. Fingolimod-associated macular edema: incidence, detection, and management. *Neurology.* 2012;78(9):672–680.

Neuromyelitis Optica

Neuromyelitis optica (NMO), also called Devic disease, is an inflammatory CNS disorder that is associated with serum aquaporin-4 immunoglobulin G (AQP4-IgG) antibodies. NMO is characterized by severe attacks of optic neuritis and longitudinally extensive transverse myelitis. NMO represents a rare cause of inflammatory white matter disease in North America; however, it accounts for almost 50% of demyelinating disorders in Asia and the West Indies. NMO can be differentiated from MS by its distinct clinical, radiographic, pathologic, and serologic features. NMO is associated with severe visual impairment; early diagnosis and aggressive treatment are important for the best chance of preserving visual and neurologic function.

Clinical presentation of neuromyelitis optica

Optic neuritis, the classic ophthalmic manifestation of NMO, is typically severe (visual acuity <20/200) and is associated with poor visual recovery. Bilateral visual symptoms, recurrent optic neuritis, poor visual outcomes, or concurrent autoimmune disease should raise a concern for NMO-related optic neuritis (see Chapter 4).

NMO may involve the optic chiasm and tracts, resulting in bitemporal or homonymous hemianopic visual field defects. Eye movement disorders such as nystagmus (upbeat,

Table 14-1 Disease-Modifying Therapies Used in the Treatment of Multiple Sclerosis

Drug	Route	MS Subtype	Dosing Frequency	Adverse Effects
Interferon β -1a (Avonex)	Intramuscular	Relapsing forms of MS, CIS	Once weekly	Flulike symptoms, liver enzyme changes, bone marrow suppression, thyroid dysfunction
Interferon β -1a (Rebif)	Subcutaneous	Relapsing forms of MS, CIS	22 mcg or 44 mcg three times weekly	Flulike symptoms, liver enzyme changes, bone marrow suppression, thyroid dysfunction
Interferon β -1b (Betaseron) (Extavia)	Subcutaneous	Relapsing forms of MS, CIS	Three times weekly	Flulike symptoms, liver enzyme changes, bone marrow suppression, thyroid dysfunction
Glatiramer acetate (Copaxone)	Subcutaneous	Relapsing forms of MS, CIS	Daily	Skin irritation, skin lipoatrophy, panic attack-like events
Natalizumab (Tysabri)	Intravenous	Relapsing forms of MS	Once monthly	Nausea, infection, liver dysfunction, PML*
Fingolimod (Gilenya)	Oral	Relapsing forms of MS	Daily	Macular edema, bradyarrhythmia, QT interval prolongation, hypertension, severe varicella-associated complications in nonimmune patients, increased risk of herpes zoster in all patients, PML (rare)
Dimethyl fumarate (Tecfidera)	Oral	Relapsing forms of MS	Twice daily	Flushing, gastrointestinal distress, lymphopenia (rare), PML (rare)
Teriflunomide (Aubagio)	Oral	Relapsing forms of MS	Once daily	Nausea, headaches, alopecia, liver dysfunction, presumed teratogenicity
Alemtuzumab (Lemtrada)	Intravenous	Relapsing forms of MS	Minimum of two cycles (baseline and year 1)	Infusion reactions, mild-moderate infections, thyroid dysfunction, idiopathic thrombocytopenic purpura, anti-glomerular basement membrane disease
Daclizumab (Zinbryta)	Subcutaneous	Relapsing forms of MS†	Monthly	Mild-moderate infections, allergic reactions, dermatitis/rash, lymphadenopathy, oropharyngeal pain, liver irritation, depression

CIS = clinically isolated syndrome, MS = multiple sclerosis, PML = progressive multifocal leukoencephalopathy.

*PML risk increases with a history of immunosuppression, JC virus positivity, and use of the drug >2 years. Risk for the entire cohort ("all-comers") is roughly 3–4/10,000.

†The US Food and Drug Administration has recommended this drug be used only if the patient manifests an inadequate therapeutic response to 2 or more other DMTs.

Table reprinted with permission from Costello F, Lee AG, Burton JM. Neuro-ophthalmologic manifestations of multiple sclerosis. Medscape Drugs & Diseases website. Available at: <http://emedicine.medscape.com/article/1214270-overview>. Accessed January 16, 2017.

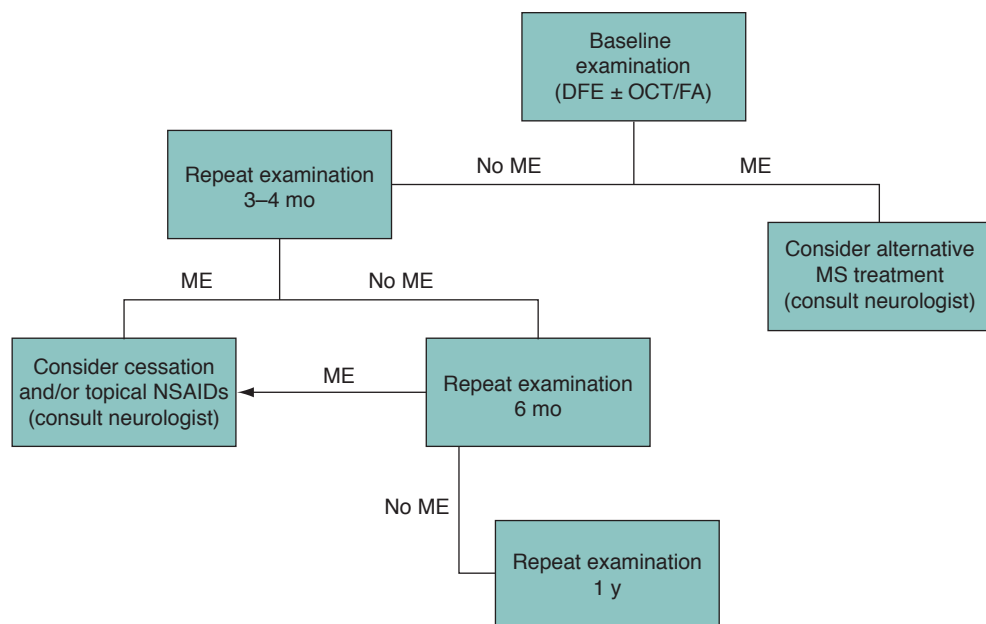


Figure 14-2 Proposed screening protocol for fingolimod-associated macular edema (FAME). Patients with visual symptoms at any time during treatment should have an additional eye examination, particularly during the initial months of treatment. DFE = dilated fundus exam; FA = fluorescein angiography; ME = macular edema; MS = multiple sclerosis; OCT = optical coherence tomography. (Adapted from Jain N, Bhatti MT. Macular edema associated with fingolimod. *EyeNet*. 2012: 43–44.)

downbeat, or mixed horizontal-torsional), internuclear ophthalmoplegia, and opsoclonus can develop secondary to brainstem lesions.

Patients with transverse myelitis may present with weakness and numbness of the limbs, deficits in sensation and motor skills, dysfunctional sphincter activities, or dysfunction of the autonomic nervous system. NMO is a central cause of refractory hiccups and vomiting due to caudal medullary lesions (the area postrema and the nucleus tractus solitarius).

Diagnosis of neuromyelitis optica

The development of the NMO-IgG (AQP4-IgG antibody) test has drastically improved our ability to diagnose NMO. However, the test is negative in approximately 25% of patients. In 2015, an international panel published revised diagnostic criteria for NMO and also recommended unifying NMO and related syndromes under the new nomenclature of neuromyelitis optica spectrum disorder (NMOSD) (see Chapter 4, Table 4-5, for criteria in diagnosing NMOSD).

CSF findings suggestive of NMO include a pleocytosis greater than 50 cells per microliter, a high percentage of polymorphonuclear cells, or the presence of eosinophils. In rare instances, CSF AQP4-IgG has been detected in seronegative patients.

Conventional MRI shows typical changes resulting from acute optic neuritis with NMO, including optic nerve enlargement and enhancement, as well as increased

T2 signal. These changes, which are often more longitudinally extensive than in MS, are frequently bilateral and may involve the optic chiasm and tracts. Brain MRI abnormalities at onset have been reported in 43%–70% of patients with NMOSD. NMO lesions are typically found in the areas surrounding the third ventricle and the cerebral aqueduct (which include the thalamus, hypothalamus, and anterior border of the midbrain), as well as the dorsal brainstem adjacent to the fourth ventricle and the corpus callosum. Extensive and confluent hemispheric white matter lesions can also be seen, occasionally mimicking posterior reversible encephalopathy syndrome (PRES; discussed later). Spinal cord MRI typically shows contiguous T2-weighted signal abnormality extending over 3 or more vertebral segments.

Kim HJ, Paul F, Lana-Peixoto MA, et al. MRI characteristics of neuromyelitis optica spectrum disorder: an international update. *Neurology*. 2015;84(11):1165–1173.

Wingerchuk DM, Banwell B, Bennett JL, et al; International Panel for NMO Diagnosis. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177–189.

Treatment of neuromyelitis optica

NMO treatment includes managing acute attacks and preventing future exacerbations. For patients experiencing an acute attack, intravenous methylprednisolone therapy (1000 mg daily for 3–5 days) remains the first-line therapy. If there is no significant clinical improvement on corticosteroids, plasma exchange has been shown to be effective and should be considered. Intravenous immunoglobulin (IVIg) has also been used to treat acute NMO exacerbations and prevent relapses. Immunosuppressive therapy (eg, azathioprine, mycophenolate, or rituximab) is generally instituted after the initial attack to lower the frequency and severity of future exacerbations. Several disease-modifying agents frequently used for treatment of MS (eg, interferon-beta, natalizumab, and fingolimod) may increase the relapse rate in patients with NMO. This phenomenon likely reflects the different immunobiology of these conditions, emphasizing the importance of accurate diagnosis in guiding optimal treatment decisions.

Kowarik MC, Soltys J, Bennett JL. The treatment of neuromyelitis optica. *J Neuroophthalmol*. 2014;34(1):70–82.

Sato DK, Lana-Peixoto MA, Fujihara K, deSeze J. Clinical spectrum and treatment of neuromyelitis optica spectrum disorders: evolution and current status. *Brain Pathol*. 2013;23(6):647–660.

Myasthenia Gravis

Myasthenia gravis (MG) is an immunologic disorder characterized by variable and fatigable weakness. Most patients with MG develop neuro-ophthalmic abnormalities. Although the disease is usually a systemic disorder, one-half of affected patients have ocular symptoms and signs at onset. The pathophysiology arises from antibodies that reduce the number of available nicotinic acetylcholine receptors. MG may be caused, unmasked, or worsened by numerous types of medications, including antiarrhythmics, statins, antibiotics, chemotherapeutic drugs, antiepileptics, quinolones, penicillamine, corticosteroids, β -blockers, and calcium channel blockers.

Clinical presentation of myasthenia gravis

The hallmarks of MG are fluctuation and fatigability (although these are not invariably present). Clinical signs and symptoms usually worsen in the evening and with use of the eyes and may improve with rest. The most common sign of MG is unilateral or bilateral ptosis. The extent of ptosis tends to vary, with the eyelid more ptotic in the evening, after exertion, or after prolonged upward gaze. Cogan eyelid twitch, elicited by having the patient initiate saccades during refixation from downgaze to upgaze, is a brief overelevation of the upper eyelid. Another eyelid sign is enhancement of ptosis; when the more ptotic eyelid is elevated manually, the less ptotic eyelid falls, in keeping with Hering's law of motor correspondence (equal and simultaneous innervation) (see Chapter 11, Fig 11-3). Fatigue of ptosis can be assessed by asking the patient to sustain upgaze for 1 minute or longer.

MG frequently causes diplopia. The diplopia may be variable, both during the day and from one day to another. The ocular motility pattern may simulate ocular motor CN paresis (usually CN VI or partial, pupil-sparing CN III palsy), internuclear ophthalmoplegia, supranuclear motility disturbances (eg, gaze palsies), or isolated muscle "palsy" (eg, isolated inferior rectus). Total ophthalmoplegia can also occur. Any changing pattern of diplopia, with or without ptosis, should suggest MG. As with ptosis, motility fatigue can also be assessed by having the patient sustain gaze in the direction of paresis. Orbicularis oculi weakness is often present in patients with ocular MG and, if present, can be diagnostically crucial in differentiating MG from other causes of external ophthalmoplegia.

Because the pupil contains muscarinic acetylcholine receptors, pupillary abnormalities are not associated with MG; if abnormalities are present, the clinician should search for another diagnosis. Systemic symptoms and signs that are associated with MG include dysarthria, dysphagia, dyspnea, hoarseness, and weakness in the mastication muscles and in the extensors of the neck, trunk, and limbs. Dysphagia and dyspnea can be life threatening and require prompt treatment. Thyroid eye disease (TED) occurs in about 5% of MG patients. The presence of exotropia and/or ptosis in a patient with TED should raise a concern for superimposed MG.

Diagnosis of myasthenia gravis

The diagnosis of MG is made clinically by identifying typical signs and symptoms, pharmacologically by overcoming the receptor block via the administration of acetylcholinesterase inhibitors, serologically by demonstrating elevated anti-acetylcholine receptor antibody titers or anti-muscle-specific kinase antibodies, and electrophysiologically by electromyography (EMG) results.

If an obvious abnormality is present on examination, results of an *edrophonium chloride* (a short-acting acetylcholinesterase inhibitor) *test*, a *sleep test*, or an *ice-pack test* can confirm the diagnosis of MG. Edrophonium chloride tests are not commonly performed in eye clinics because rare but serious adverse effects from administration of the drug can occur, including bradycardia, bronchospasm, cholinergic crisis, respiratory arrest, or syncopal episodes. Thus, consultation with the primary physician is suggested before performing the test on patients with a history of cardiac or pulmonary disease. Atropine sulfate (0.4–0.6 mg) should be available immediately in case it is needed. Some physicians pretreat with atropine (0.4 mg subcutaneously) before administering the edrophonium.

Patients should also be warned of the possibility of the medication's short-lived but often discomforting adverse reactions, including fasciculations, sweating, lacrimation, abdominal cramping, nausea, vomiting, and salivation. In most protocols, a small test dose of 2 mg (0.2 mL) edrophonium is first injected intravenously, and the patient is observed for 60 seconds. If the symptoms disappear or decrease (for example, the eyelid elevates or motility improves), the test result is considered positive and can be discontinued. If no response is elicited, additional doses of 4 mg, up to a total of 10 mg, are given. When the ocular symptom is marked (eg, complete ptosis), the endpoint (eyelid elevation) is often dramatic. However, a subtle deficit, such as minimal diplopia, may require use of other means to better define the endpoint. Maddox rod tests with prisms or diplopia fields may be performed before and after edrophonium (see Chapter 7). False-positive responses are rare. A negative test result does not exclude a diagnosis of MG, and repeat testing at a later date may be needed.

An alternative to the edrophonium test is the *neostigmine methylsulfate test*. This test is particularly useful for children and for adults without ptosis who may require a longer observation period for accurate ocular alignment measurements than that allowed by edrophonium testing. Adverse reactions are similar to those for edrophonium, the most frequent of which are salivation, fasciculations, and gastrointestinal discomfort. Intramuscular neostigmine and atropine are injected concurrently. A positive test result produces improvement of signs within 30–45 minutes.

The *sleep test* is a safe, simple office test that eliminates the need for edrophonium testing in many patients. After the baseline deficit has been documented (eg, measurements of ptosis, motility disturbance), the patient rests quietly with eyes closed for 30 minutes. The measurements are repeated immediately after the patient “wakes up” and opens his or her eyes. Improvement after rest is highly suggestive of MG.

The *ice-pack test* is often helpful for diagnosing MG, but only if the patient has ptosis. An ice pack is placed over the patient's lightly closed eyes for 2 minutes. Improvement of ptosis occurs in most patients with MG (Fig 14-3); however, the cooling effect may be insufficient to overcome the severe weakness in patients with *complete* myasthenic ptosis.

Other diagnostic tests for MG include electrophysiologic testing and serum assays for anti-acetylcholine receptor (AChR) antibodies or anti-muscle-specific kinase (MuSK) antibodies. There are 3 types of commercially available AChR antibody tests: binding, blocking, and modulating. Tests for binding antibodies are usually requested first, because these highly specific antibodies (near 100% specificity) are detected in approximately 90% of patients with generalized MG and in 50%–70% of patients with ocular MG. Blocking

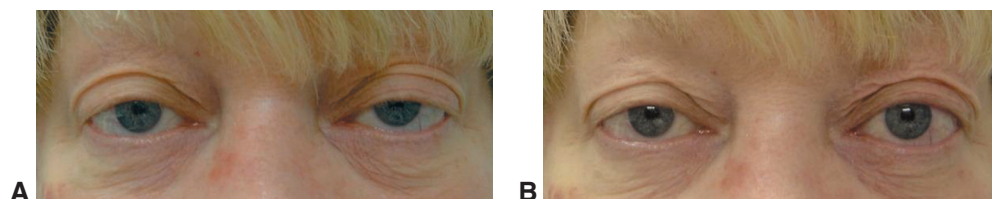


Figure 14-3 Ice-pack test. **A**, A 57-year-old woman with myasthenia gravis presented with moderate, variable left ptosis. **B**, The left ptosis improved after a 2-minute ice-pack test. (Courtesy of Karl C. Golnik, MD.)

antibodies are rarely present (1%) without binding antibodies. Modulating antibodies are present as frequently as binding antibodies. Blocking and modulating antibody testing is usually reserved for patients who test negative for the binding antibody and for whom MG is still suspected. An assay for MuSK antibodies may confirm an MG diagnosis in some patients who do not have AChR antibodies. MuSK-positive patients tend to have prominent bulbar weakness (eg, dysphagia, dysphonia, chewing difficulties) and will present with purely ocular manifestations only in rare instances.

Electromyographic repetitive nerve stimulation shows a characteristic decremental response in many patients with systemic MG. Single-fiber electromyography is most sensitive for MG. All patients with MG should be investigated radiologically for thymomas, which are observed on computed tomography (CT) scans in 10% of these patients. Malignant thymomas are present in a small percentage of patients. Because there is a high coexistence of MG with other autoimmune disorders, serologic testing should be done for thyroid dysfunction and systemic lupus erythematosus.

Gwathmey KG, Burns TM. Myasthenia gravis. *Semin Neurol*. 2015;35(4):327–339.

Mercelis R, Merckaert V. Diagnostic utility of stimulated single-fiber electromyography of the orbicularis oculi muscle in patients with suspected ocular myasthenia. *Muscle Nerve*. 2011; 43(2):168–170.

Peeler CE, De Lott LB, Nagia L, Lemos J, Eggenberger ER, Cornblath WT. Clinical utility of acetylcholine receptor antibody testing in ocular myasthenia gravis. *JAMA Neurol*. 2015; 72(10):1170–1174.

Treatment of myasthenia gravis

Symptomatic, nonpharmacologic treatment for ptosis or diplopia may include use of a patch, a ptosis crutch, or prisms; however, prisms are typically used when the variability is small and with the understanding that the treatment is not always helpful. Pharmacologic treatment for MG includes the use of acetylcholinesterase inhibitors (eg, neostigmine and pyridostigmine), corticosteroids, and other immunosuppressant drugs. Thymectomy is performed in patients with a thymoma and should be considered in patients with generalized MG with or without thymic abnormalities. Short-term therapies such as IVIg or plasmapheresis are occasionally necessary.

MG is a systemic disease with disastrous potential. Although purely ocular MG does exist, systemic MG will develop over the next 2 years in up to 20% of patients who present with ocular MG. Because MG patients may develop respiratory and other life-threatening manifestations, it is prudent to manage their care in cooperation with a neurologist. If ocular signs remain truly isolated for more than 2 years, the disease is likely to remain clinically ocular; nevertheless, late conversion to generalized MG is possible.

Mantegazza R, Bonanno S, Camera G, Antozzi C. Current and emerging therapies for the treatment of myasthenia gravis. *Neuropsychiatr Dis Treat*. 2011;7:151–160.

Thyroid Eye Disease

Thyroid eye disease (TED), also known as *thyroid-associated orbitopathy* and *Graves ophthalmopathy*, is an autoimmune inflammatory disorder. Although the underlying cause remains unknown, the clinical signs are characteristic and may include a combination of eyelid retraction, eyelid lag, proptosis, restrictive extraocular myopathy, and optic

neuropathy. Refer to Chapter 4 in this volume as well as BCSC Section 7, *Oculofacial Plastic and Orbital Surgery*, for further discussion of TED.

Sarcoidosis

Sarcoidosis is a multisystem, noncaseating granulomatous inflammation commonly diagnosed in young adults aged 20–40 years. In North America, the annual incidence for blacks is about 3 times the incidence for whites, and the disease is more common in women than in men. Although the lungs are involved most frequently, the eyes, heart, lacrimal glands, liver, lymph nodes, skin, and musculoskeletal system are also commonly affected. Neurologic manifestations, which occur in 5%–15% of patients, include CN involvement, meningitis, hydrocephalus, hypothalamic and pituitary involvement, encephalopathy, seizures, dural venous thrombosis, vasculitis, myelopathy, and peripheral neuropathy. However, 30%–60% of cases may be discovered incidentally on a routine chest radiograph.

Krumholz A, Stern BJ. Neurologic manifestations of sarcoidosis. *Handb Clin Neurol*. 2014; 119:305–333.

Intraocular manifestations of sarcoidosis

Iritis, cataract, vitritis, retinal vasculitis (“candlewax drippings”), and chorioretinitis can occur in sarcoidosis. For further discussion of these manifestations, see BCSC Section 9, *Uveitis and Ocular Inflammation*, and Section 12, *Retina and Vitreous*.

Acharya NR, Gonzales JA. Ocular sarcoidosis. *Focal Points: Clinical Modules for Ophthalmologists*. San Francisco: American Academy of Ophthalmology; 2014, module 10.

Neuro-ophthalmic manifestations of sarcoidosis

After the facial nerve, the optic nerve is the CN most frequently affected by sarcoidosis; it may manifest as either a papillitis or retrobulbar optic neuropathy. Less commonly, a sarcoid granuloma may occur at the optic nerve head (ONH) (see Chapter 4, Fig 4-13). Infrequently, sarcoidosis may cause neuroretinitis, optic perineuritis, or papilledema. Bitemporal and homonymous visual field defects may also occur from chiasmal and retrochiasmal visual pathway involvement. Sarcoidosis can also cause ocular motor CN palsy, gaze palsy, and a variety of pupillary abnormalities, including tonic pupil, Horner syndrome, and Argyll Robertson pupil.

Diagnosis and treatment of sarcoidosis

The diagnostic criteria for sarcoidosis include clinical symptoms and signs along with supporting, radiographic, and/or histologic results. Although most patients with neurosarcoidosis exhibit abnormalities on MRI scan, about 18% do not. The most common neuroimaging abnormalities are meningeal and leptomeningeal enhancing lesions. However, none of the abnormalities observed on MRI scan are specific for sarcoidosis, and establishing a definite diagnosis can be difficult.

Serum markers such as angiotensin-converting enzyme (ACE) and lysozyme have been associated with sarcoidosis. The sensitivity and specificity of ACE as a diagnostic test is 60% and 70% respectively. Hypercalcemia is seen in about 10%–13% of patients, whereas hypercalciuria is 3 times more common. A chest radiograph, usually a high-resolution CT scan, is typically obtained because of the frequent pulmonary involvement

associated with sarcoidosis. Gallium scanning is a sensitive but nonspecific indicator of active inflammation in patients with sarcoidosis. Fluorodeoxyglucose positron emission tomography (FDG-PET) is a sensitive method to assess inflammatory activity and the extent of disease; it is especially helpful in assessing persistently symptomatic patients without abnormal serologic signs. Histologic studies of involved conjunctiva, lacrimal glands, lymph nodes, or lungs may demonstrate noncaseating granulomas.

Corticosteroids and other immunomodulatory therapies (in particular, methotrexate and tumor necrosis factor [TNF] blockers) are the mainstays of treatment.

Frohman LP. Treatment of neuro-ophthalmic sarcoidosis. *J Neuroophthalmol*. 2015;35(1):65–72.

Phillips YL, Eggenberger ER. Neuro-ophthalmic sarcoidosis. *Curr Opin Ophthalmol*. 2010;21(6):423–429.

Inherited Disorders With Neuro-Ophthalmic Signs

Numerous inherited disorders result in neuro-ophthalmic signs. Certain myopathies and neurocutaneous syndromes (phakomatoses) are the most common inherited systemic conditions. Inherited optic neuropathies are discussed in Chapter 4.

Myopathies

The extraocular muscles are affected by several inherited conditions that result in mitochondrial dysfunction.

Chronic progressive external ophthalmoplegia

Chronic progressive external ophthalmoplegia (CPEO) is an inherited mitochondrial myopathy characterized by slowly progressive, symmetric ophthalmoplegia with or without ptosis (Video 14-1; Fig 14-4). The majority of patients with CPEO have mitochondrial DNA (mtDNA) deletions or point mutations, but nuclear DNA mutations can also cause CPEO. Thus, the mode of inheritance can be mitochondrial (maternal), autosomal, or sporadic (most common), and the disorder may not be transmissible to the next generation. Patients often initially present with ptosis and do not generally complain of diplopia. However, the majority of patients have visual impairment and difficulty with reading. At presentation, myasthenia gravis may be considered in the differential diagnosis, but in contrast to patients with CPEO, MG patients typically have variable signs and symptoms. Clinical findings usually develop in patients between 18–40 years of age. Systemic symptoms may include generalized muscle weakness. Genetic testing is available for detection of abnormalities in the mtDNA. Histologic examination of muscle biopsy specimens shows the characteristic “ragged red fibers” (Fig 14-5) and mitochondrial proliferation, and electron microscopic studies show inclusion body abnormalities of the affected mitochondria.



VIDEO 14-1 Chronic bilateral external ophthalmoplegia with bilateral ptosis.

Courtesy of M. Tariq Bhatti, MD.

Access all Section 5 videos at www.aao.org/bcscvideo_section05.



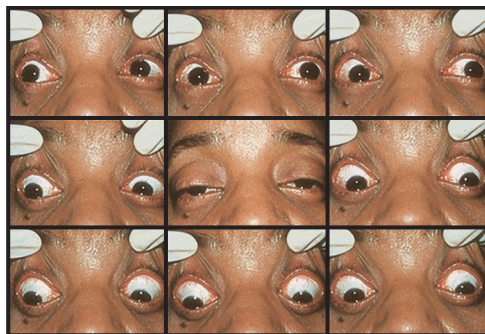


Figure 14-4 Chronic progressive external ophthalmoplegia in a 42-year-old with a 2-year history of progressive ptosis and bilateral external ophthalmoplegia. (Courtesy of Steven A. Newman, MD.)

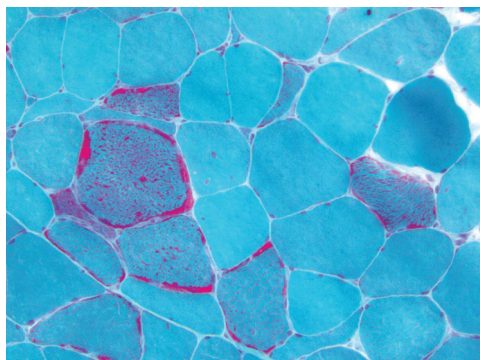


Figure 14-5 Histologic examination of a muscle biopsy specimen shows ragged red fibers (modified Gomori trichrome stain). (Courtesy of Marjorie R. Grafe, MD.)

Kearns-Sayre syndrome is also an inherited mitochondrial myopathy. It includes CPEO, pigmentary retinopathy, and cardiac conduction abnormalities, and it variably includes cerebellar ataxia, deafness, and elevated CSF protein levels. Cardiac evaluation is essential to rule out conduction defects; this evaluation should be obtained for all patients with CPEO.

Yu Wai Man CY, Smith T, Chinnery PF, Turnbull DM, Griffiths PG. Assessment of visual function in chronic progressive external ophthalmoplegia. *Eye (Lond)*. 2006;20(5):564–568.

Oculopharyngeal dystrophy

Oculopharyngeal dystrophy is a hereditary condition, usually autosomal dominant, with onset in the fifth and sixth decades of life. The typical presentation is progressive bilateral ptosis followed by dysphagia and proximal muscle weakness. Most patients have an external ophthalmoplegia that, when asymmetric, may be accompanied by diplopia. Pathologic studies show a vacuolar myopathy. The disease is classically observed in patients of French Canadian ancestry. The only causative mutation described to date is a triplet repeat expansion consisting of 2–7 additional base triplets in a repeat sequence in exon 1 of the polyadenine binding protein, nuclear 1 gene (*PABPN1*), located on chromosome 14.

Myotonic dystrophy

Myotonic dystrophy, a dominantly inherited multisystem disorder, also produces ophthalmoplegia that may mimic CPEO. Two types have been identified: type 1, resulting from mutation on chromosome 19, and type 2, resulting from mutation on chromosome 3. Symptoms usually start in late childhood or early adulthood with myotonia that is exacerbated by excitement, cold, and fatigue. The myotonia can be easily detected by asking the patient to shake hands; the patient will not be able to quickly release his or her grasp. This myopathy is unusual in that it affects distal limb musculature first. Wasting of the temporalis and masseter muscles produces the typical “hatchet face.” The myopathic facies, frontal balding, and ptosis cause a distinct and remarkably characteristic appearance.

Ocular findings include ptosis, pigmentary retinopathy, ophthalmoparesis, and polychromatic lenticular deposits (“Christmas tree” cataracts). The pupils are miotic and respond sluggishly to light. Other features of this dystrophy include low intelligence, insulin resistance, hearing loss, cardiomyopathy, cardiac conduction abnormalities, testicular atrophy, and uterine atony. Electromyographic studies can demonstrate characteristic myotonic discharges, and genetic testing can confirm the diagnosis of myotonic dystrophy.

Turner C, Hilton-Jones D. The myotonic dystrophies: diagnosis and management. *J Neurol Neurosurg Psychiatry*. 2010;81(4):358–367.

Neurocutaneous Syndromes

Neurocutaneous syndromes, or *phakomatoses*, are disorders characterized by the presence of hamartomas involving different organ systems, such as the skin, eyes, CNS, and viscera. Phakomatoses are inconsistently defined, and there is a lack of consensus about which conditions should be considered neurocutaneous syndromes. Four major disorders have traditionally been designated phakomatoses:

1. neurofibromatosis type 1 (von Recklinghausen disease, Fig 14-6) and type 2
2. tuberous sclerosis (Bourneville disease, Fig 14-7)
3. angiomas of the retina and cerebellum (von Hippel–Lindau disease, Fig 14-8)
4. ataxia-telangiectasia (Louis-Bar syndrome, Fig 14-9)

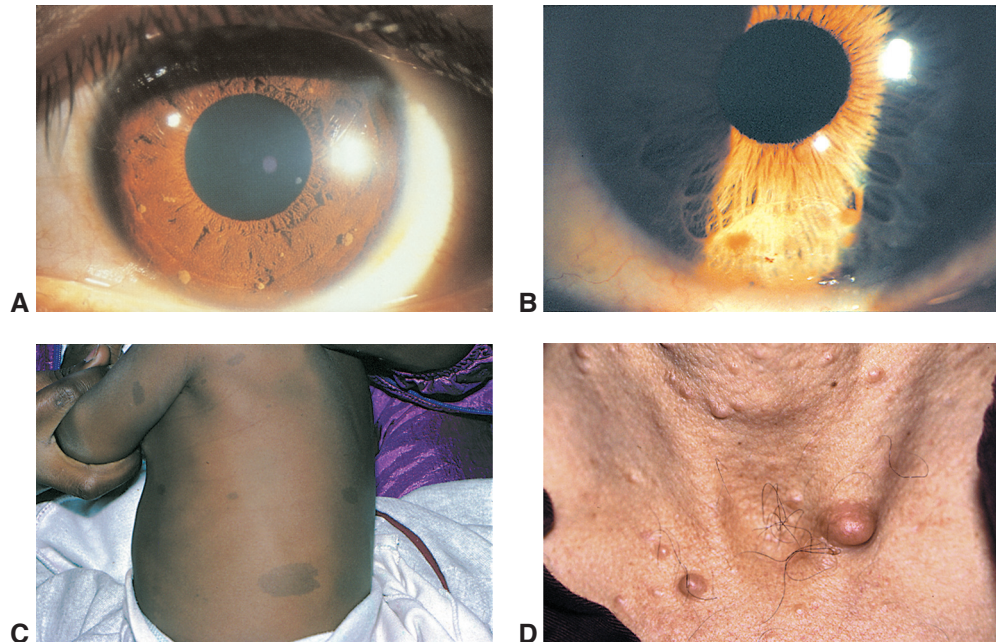


Figure 14-6 The most common ocular finding in neurofibromatosis type 1 (NF1) is the presence of iris (Lisch) nodules. These are often light colored in a patient with dark irides (**A**) but may be relatively darker in patients with light irides (**B**). The diagnosis is often suggested by cutaneous findings, including café-au-lait spots (**C**) or skin neurofibromas (**D**). (Part A courtesy of Mark J. Greenwald, MD; parts B–D courtesy of Steven A. Newman, MD.)

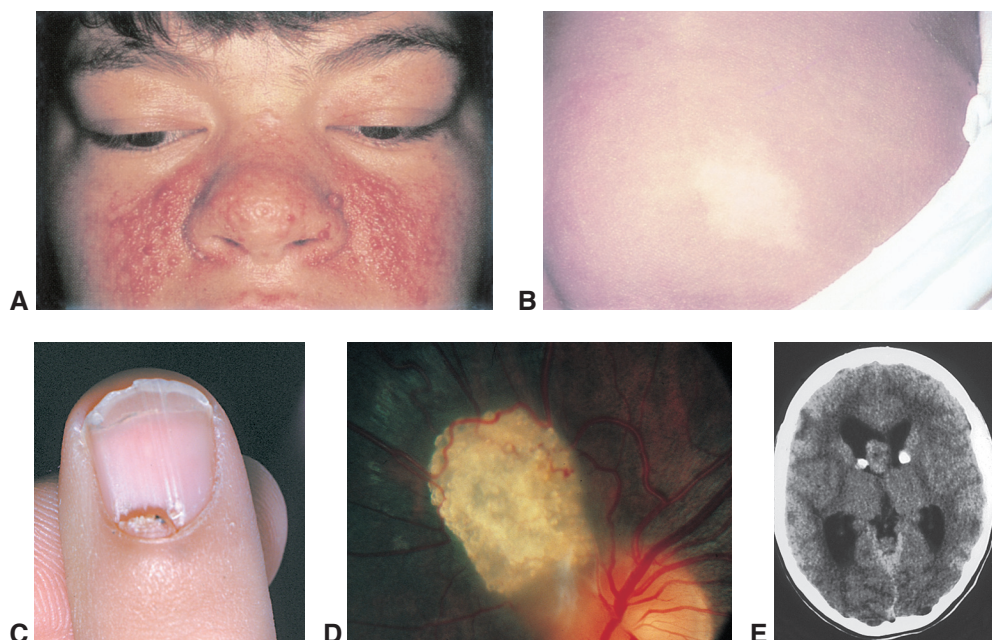


Figure 14-7 Tuberosclerosis. **A**, Hamartomatous angiofibromas (previously called adenoma sebaceum) are a hallmark of this syndrome and involve the cheek, particularly in the area of the nasolabial fold. Other classic skin findings include the presence of an ash-leaf spot (**B**), best observed with ultraviolet light, and subungual lesions (**C**). **D**, Ophthalmic findings include the presence of astrocytic hamartomas on fundusoscopic examination. **E**, Intracranial hamartomas often line the subependymal surface. They frequently calcify, becoming obvious on computed tomography (CT) scan. (Parts A, B courtesy of Mark J. Greenwald, MD; parts C, E courtesy of Steven A. Newman, MD; part D reprinted from Kline LB, Foroozan R, eds. *Optic Nerve Disorders*. 2nd ed. *Ophthalmology Monographs* 10. New York: Oxford University Press, in cooperation with the American Academy of Ophthalmology; 2007:164.)



Figure 14-8 Fundus photograph of a patient with von Hippel-Lindau disease, showing a characteristic hemangioblastoma of the retina. (Courtesy of Steven A. Newman, MD.)

Encephalofacial angiomatosis (Sturge-Weber syndrome, Fig 14-10), racemose angioma (Wyburn-Mason syndrome, Fig 14-11), incontinentia pigmenti, and Klippel-Trénaunay-Weber syndrome are among the other conditions sometimes classified as phakomatoses.

These disorders, which are discussed at length in BCSC Section 6, *Pediatric Ophthalmology and Strabismus*, are characterized by tumors formed from normal tissue elements: hamartomas and choristomas. A *hamartoma* is composed of elements normally found at the involved site; hamartomas are not true neoplasms, because they are anomalies of

Figure 14-9 Photograph of the left eye of a child with ataxia-telangiectasia, showing abnormally dilated and tortuous conjunctival vessels. (Courtesy of Mark J. Greenwald, MD.)

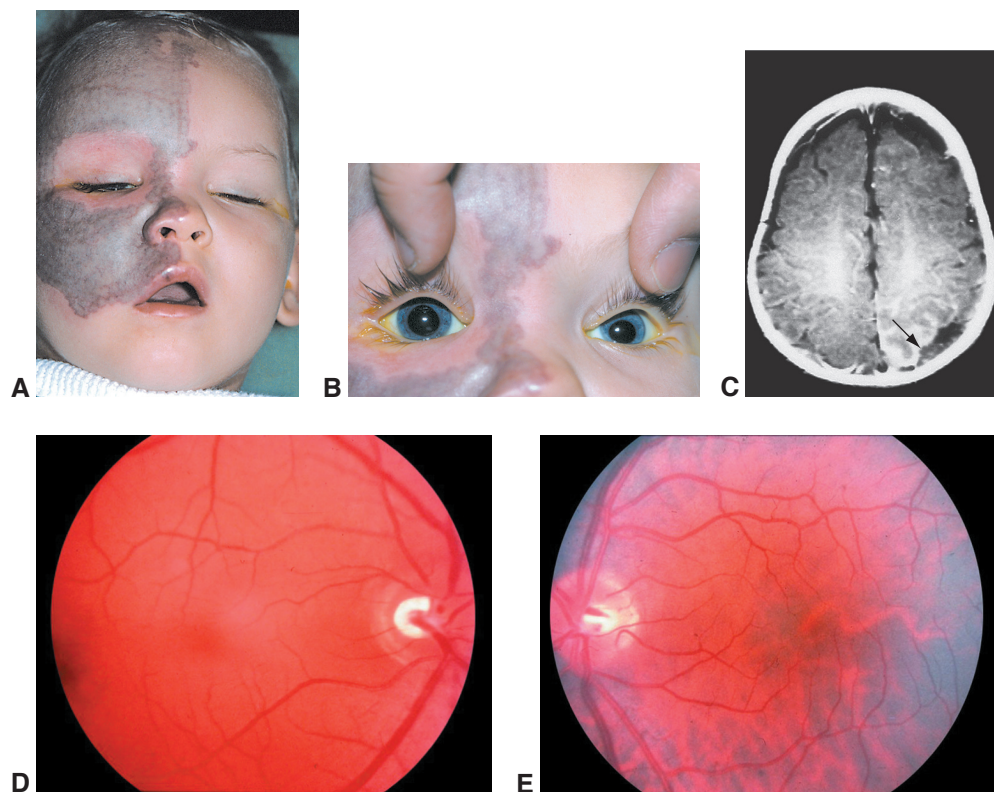
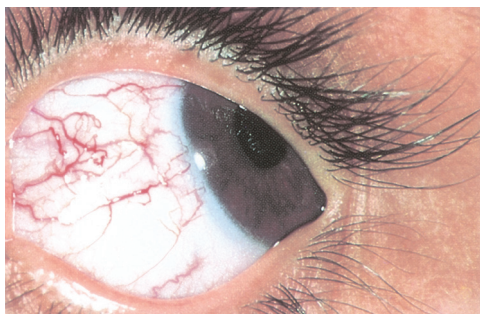


Figure 14-10 Sturge-Weber syndrome. **A**, This 1-year-old exhibits a port-wine stain involving the V₁ and V₂ distributions on the right side, a classic finding in this syndrome. These patients often have congenital glaucoma. **B**, In an infant with congenital glaucoma, the globe may enlarge significantly (buphthalmos). **C**, MRI scan shows cortical vascular malformations following the gyral pattern (arrow). Diffuse choroidal hemangiomas may also occur, causing increased hyperemia and redness of the choroid. **D**, Fundus photograph showing choroidal hemangioma and **E**, the contralateral normal eye. (Parts A, B courtesy of Steven A. Newman, MD; part C courtesy of Mark J. Greenwald, MD; parts D, E courtesy of James J. Augsburger, MD.)

tissue formation that lack the capability for limitless proliferation. The glial retinal tumors of tuberous sclerosis are a type of hamartoma. *Choristomas* are tumor-like growths composed of tissue not normally present at the site of growth. Some phakomatous lesions are neoplasms, but the majority are hamartomas or choristomas.



Figure 14-11 Fundus photograph shows an arteriovenous malformation (racemose angioma) of the retina in a patient with Wyburn-Mason syndrome. (Courtesy of Mark J. Greenwald, MD.)

Table 14-2 summarizes the important features of the most common phakomatoses.

Ullrich NJ. Neurocutaneous syndromes and brain tumors. *J Child Neurol.* 2016;31(12):1399–1411.

Selected Neuro-Ophthalmic Disorders Associated With Pregnancy

During pregnancy or the postpartum period, several neuro-ophthalmic abnormalities can be exacerbated or occur with greater frequency, including cerebral venous thrombosis (CVT), idiopathic intracranial hypertension (IIH), pituitary apoplexy, and lymphocytic hypophysitis. CVT is discussed later in this chapter (see the section Cerebrovascular Disorders), and IIH and pituitary apoplexy are discussed in Chapter 4. Preexisting pituitary macroadenomas, meningiomas, schwannomas, and orbital and choroidal hemangiomas can also undergo rapid expansion during pregnancy.

A number of cranial neuropathies have been reported during pregnancy, most frequently involving the CN VII followed by the CN VI. These cranial neuropathies are thought to result from an increase in interstitial fluid around the nerve, causing compression. Hypercoagulopathy and hypertension have also been proposed as potential causes.

Severe preeclampsia/eclampsia can lead to various ophthalmic manifestations, including serous retinal detachment, choroidal infarction, retinal vascular narrowing, and retinal artery vasospasm or occlusion. The optic nerve may become edematous secondary to systemic hypertension, intracranial hypertension, or ischemic optic neuropathy. Disorders of higher cortical function, such as alexia, simultagnosia, and cortical blindness have also been reported. In addition, PRES may develop in the context of preeclampsia/eclampsia (see the following section).

Digre KB. Neuro-ophthalmology and pregnancy: what does a neuro-ophthalmologist need to know? *J Neuroophthalmol.* 2011;31(4):381–387.

Posterior Reversible Encephalopathy Syndrome

PRES is characterized by headache, altered mental status, seizures, and visual disturbances (blurred vision, homonymous visual field loss, cortical blindness, photopsias, and visual hallucinations). MRI shows T2-hyperintense vasogenic edema involving the white matter of the cerebral posterior regions, especially the parieto-occipital lobes; however, the frontal

Table 14-2 Neurocutaneous Syndromes

	Neurofibromatosis Type 1 (NF1)	Neurofibromatosis Type 2 (NF2)	Tuberous Sclerosis (TS)	Retinal and Cerebellum Angiomatosis	Ataxia-Telangiectasia (AT)	Encephalofacial Angiomatosis	Racemose Angioma
Common name	von Recklinghausen	Bilateral acoustic neurofibromatosis	Bourneville disease	von Hippel-Lindau (VHL) disease	Louis-Bar syndrome	Sturge-Weber syndrome (SWS)	Wyburn-Mason syndrome
Chromosome location	17q11.2	22q12.2	9q34 (<i>TSC1</i>) 16q13.3 (<i>TSC2</i>)	3p25.3	11q22.3	Not genetically transmitted	Not genetically transmitted
Gene name	Neurofibromin 1	Neurofibromin 2	<i>TSC1</i> , hamartin <i>TSC2</i> , tuberin	<i>VHL</i>	<i>ATM</i>		
Inheritance pattern	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive	Sporadic	Sporadic
Classic manifestations	Lisch nodules Fibroma molluscum Plexiform neurofibroma Café-au-lait spots Optic pathway glioma Osseous defects including sphenoid wing dysplasia Hyperpigmented choroidal lesions	Acoustic neuromas Meningioma(s) Posterior subcapsular cataract Epiretinal membrane Retinal hamartoma	Facial angiofibromas Ungual fibromas Shagreen patches Ash-leaf spots Retinal and intracranial astrocytic hamartomas ("brain stones," often calcified) Seizures Cardiac rhabdomyoma Renal hamartomas or cysts Cognitive impairment	Retinal hemangioblastoma that is often multiple and bilateral; can cause serous retinal detachment Cerebellar hemangioblastoma Pheochromocytomas Renal cysts or renal cell carcinoma	Cerebellar ataxia Conjunctival telangiectasia Poor initiation of saccades associated with head thrusts Horizontal and vertical supranuclear gaze palsies Increased risk of malignancies Recurrent respiratory tract infections	Hemifacial nevus flammeus (port-wine stain) Ipsilateral lepto-meningeal vascular malformation with subcortical calcifications Choroidal hemangioma Glaucoma Seizures Focal neurologic deficits	Intracranial arteriovenous malformation (AVM) Ipsilateral retinal AVM (racemose angioma) Spontaneous intracranial hemorrhage

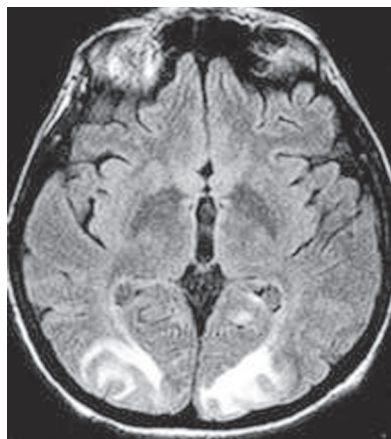


Figure 14-12 Axial FLAIR MRI scan shows reversible bilateral posterior circulation signal abnormalities in a patient with transient cortical blindness and pre-eclampsia. (Courtesy of Lanning B. Kline, MD.)

and temporal lobes, basal ganglia, and brainstem may be involved as well (Fig 14-12). A variety of conditions can predispose a patient to PRES; common causes include acute hypertension, preeclampsia/eclampsia, immunosuppressive drugs (eg, cyclosporine, tacrolimus), renal disease, sepsis, and multiorgan dysfunction syndrome. It has been less commonly reported in patients with autoimmune disease. The abnormalities visible on neuroimaging are reversible, and the visual prognosis is usually excellent. The underlying pathophysiology of PRES remains elusive.

Fugate JE, Claassen DO, Cloft HJ, Kallmes DE, Kozak OS, Rabinstein AA. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. *Mayo Clin Proc.* 2010; 85(5):427–432.

Lymphocytic Hypophysitis

Lymphocytic hypophysitis is a rare neuroendocrine disorder characterized by autoimmune inflammation of the pituitary gland, with various degrees of pituitary dysfunction, including permanent hypopituitarism. Histologic findings consist of an initial monoclonal lymphocytic infiltrate, which can heal with minimal sequelae or progress to fibrosis. Ophthalmic manifestations include chiasmal visual field defects secondary to suprasellar extension or, less frequently, diplopia due to invasion of cavernous sinuses. Imaging characteristics and endocrine testing are not specific. The diagnosis should be suspected if a woman who is pregnant or in the peripartum period presents with headache, bitemporal visual field defects, and changes in 1 or more pituitary hormones. Corticosteroids and other immunosuppressive drugs may be needed in some patients. Surgical treatment is typically required if vision is compromised.

Cerebrovascular Disorders

Although a comprehensive discussion of cerebrovascular disorders is beyond the scope of this text, the following sections give an overview of common conditions that cause neuro-ophthalmic signs and symptoms.

Transient Visual Loss

Transient neurologic or ophthalmic symptoms in middle-aged or elderly patients suggest a vascular origin. Localization of the symptoms and signs determines whether they result from ischemia in the vertebrobasilar or the carotid artery territory. Although recurrent cerebrovascular ischemia is a concern, the major cause of death in these patients is coronary artery disease. Thus, efforts should be made to control risk factors for cardiovascular disease, such as hypertension, diabetes mellitus, and hyperlipidemias, accompanied by cessation of smoking. Diagnostic and therapeutic efforts are directed at the cerebrovascular circulation. Carotid system disorders whose main symptom is transient visual loss are discussed in Chapter 5.

Vertebrobasilar System Disease

The vertebrobasilar arterial system (posterior circulation) is composed of the vertebral, basilar, and posterior cerebral arteries. These blood vessels supply the occipital cortex, brainstem, and cerebellum.

Clinical presentation of vertebrobasilar insufficiency

Patients with vertebrobasilar insufficiency often present to the ophthalmologist first, because ocular motor and visual symptoms are prominent (Fig 14-13). Nonophthalmic symptoms of *transient ischemic attacks (TIAs)* in the vertebrobasilar system include

- ataxia, imbalance, or staggering
- vertigo combined with other brainstem symptoms such as deafness or vomiting
- transient dysarthria and dysphagia
- hemiparesis, hemiplegia, and hemisensory disturbances
- drop attacks (patient suddenly falls to the ground with no warning and no loss of consciousness)

Bilateral blurring or dimming of vision occurs almost as frequently as vertigo. The patient may report sudden bilateral graying or whiting out of vision. These episodes of dimming may last seconds to minutes and may be accompanied by flickering or flashing stars. Photopsias may occur, closely mimicking the scintillating scotomata of migraine. These attacks are frequently repetitive and may occur alone or in combination with the other transient symptoms of vertebrobasilar insufficiency. Migraine (discussed in Chapter 12) can produce similar symptoms, with or without an associated headache.

Homonymous visual field changes without other neurologic symptoms suggest involvement of the posterior circulation. Highly congruous homonymous visual field defects without other systemic symptoms are typical of occipital lobe infarcts. Patients who report reading difficulties without an obvious cause should undergo a careful visual field and Amsler grid examination in search of centrally located congruous homonymous visual field defects.

Chapter 4 details the visual manifestations of cortical infarction. Cerebral and cortical blindness, caused by bilateral occipital lobe lesions, is characterized by amaurosis,

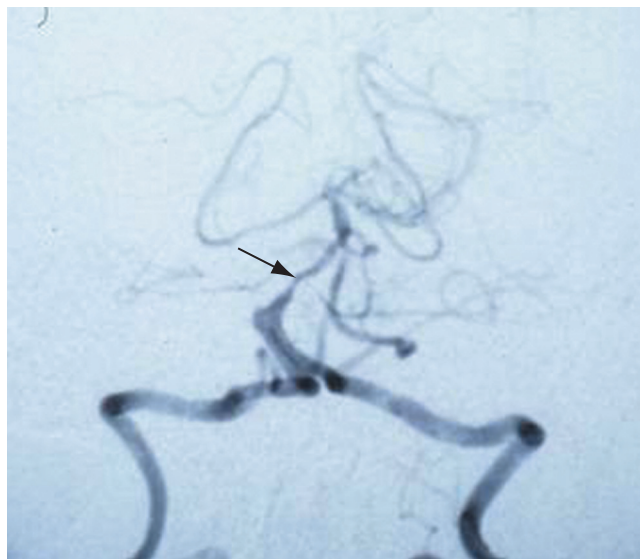


Figure 14-13 A 58-year-old woman had a sudden onset of diplopia and vertigo. Examination revealed a right CN III palsy and ataxia. Symptoms and signs resolved over 24 hours. This cerebral angiogram shows marked stenosis of the basilar artery (*arrow*). (Courtesy of Karl C. Golnik, MD.)

normally reactive pupils, and an unremarkable fundus appearance. Frequently, patients with cerebral blindness will deny their blindness (Anton syndrome; see Chapter 6).

Ocular motor disturbances are common with vertebrobasilar insufficiency, and diplopia is a frequent complaint. Examination may reveal horizontal or vertical gaze palsies, internuclear ophthalmoplegia, skew deviation, ocular motor CN palsies, or nystagmus. An ipsilateral, central Horner syndrome may be present with pontine or medullary infarcts (Wallenberg syndrome).

Levin LA. Topical diagnosis of chiasmal and retrochiasmal disorders. In: Miller NR, Newman NJ, Biousse V, Kerrison JB, eds. *Walsh and Hoyt's Clinical Neuro-Ophthalmology*. Vol 1. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2005:539–554.

Etiologies of posterior circulation ischemia

The most frequent causes of vertebrobasilar TIAs and stroke are atheromatous occlusion, hypertensive vascular disease (lacunar infarction), microembolization (either from the vertebrobasilar system or from the heart), fluctuations in cardiac output, and arterial dissection. The following conditions have all been associated with symptoms and signs of vertebrobasilar ischemia: polycythemia, hypercoagulable states, anemia, vasospasm, and congenital aplasia or hypoplasia of a vertebral or posterior communicating artery. Mechanical factors such as cervical spondylosis and chiropractic manipulation of the cervical spine have also been implicated in vertebrobasilar occlusions resulting in severe neurologic deficits. A less common cause of vertebrobasilar dysfunction is a reversal of blood flow in the vertebral artery (*subclavian steal*); this reversal is caused by a proximal occlusion of the subclavian artery that produces an unusual alteration in the direction of flow

in the ipsilateral vertebral artery. Lowered pressure in the distal segment of the subclavian artery can siphon, or “steal,” blood from the vertebral artery and produce fluctuating symptoms of vertebrobasilar artery insufficiency.

Investigation of posterior circulation ischemia

The evaluation for posterior circulation ischemia is similar to the medical workup for carotid system disease. Neuroimaging is typically performed on all patients with homonymous visual field defects and other signs of brainstem or cerebellar dysfunction. Magnetic resonance angiography (MRA) and computed tomographic arteriography (CTA) are the best noninvasive methods for evaluating the posterior circulation. Carotid Doppler imaging is not sufficient for evaluating suspected posterior circulation symptoms. Sometimes conventional angiography is necessary to visualize the aortic arch, the configuration of the vertebrobasilar vessels, and the extent of filling from the anterior circulation through the circle of Willis.

The clinician is much less likely to find a treatable structural vascular abnormality with posterior circulation ischemia than with carotid system disease. The evaluation of these patients generally emphasizes a search for underlying cardiac or systemic disorders, including hypercholesterolemia, hypertension, diabetes mellitus, and postural hypotension. Cardiac evaluation should also include echocardiography.

Markus HS, van der Worp HB, Rothwell PM. Posterior circulation ischaemic stroke and transient ischaemic attack: diagnosis, investigation, and secondary prevention. *Lancet Neurol.* 2013;12(10):989–998.

Treatment of vertebrobasilar ischemia

Most patients with vertebrobasilar TIAs are treated with statins and antiplatelet therapy or anticoagulants. Intravascular stent placement can be used in select patients with symptomatic vertebrobasilar stenosis who have failed maximal medical therapy.

Cerebral Aneurysms

Cerebral aneurysms are localized dilations of the vessel wall. They are present in approximately 5% of the population but rarely become symptomatic before 20 years of age. Cerebral aneurysms may be an isolated finding and are commonly associated with hypertension. Less common predisposing conditions include arteriovenous malformations (AVMs), coarctation of aorta, polycystic kidney disease, and connective tissue diseases (eg, fibromuscular dysplasia, Marfan syndrome, and Ehlers-Danlos syndrome). A familial occurrence is possible, and tobacco use is a risk factor. Among patients with cerebral aneurysm, 10% will have more than 1.

Figure 14-14 shows possible locations for cerebral aneurysms. The most common type of intracranial aneurysm is the saccular, or “berry,” aneurysm that arises at arterial bifurcations. Of these aneurysms, 90% are supratentorial and 10% are infratentorial. Aneurysms arising from the internal carotid artery and basilar artery may produce neuro-ophthalmic manifestations. In general, aneurysms larger than 10 mm are most likely to rupture. If they are 25 mm or larger, they are termed “giant aneurysms.” Because high

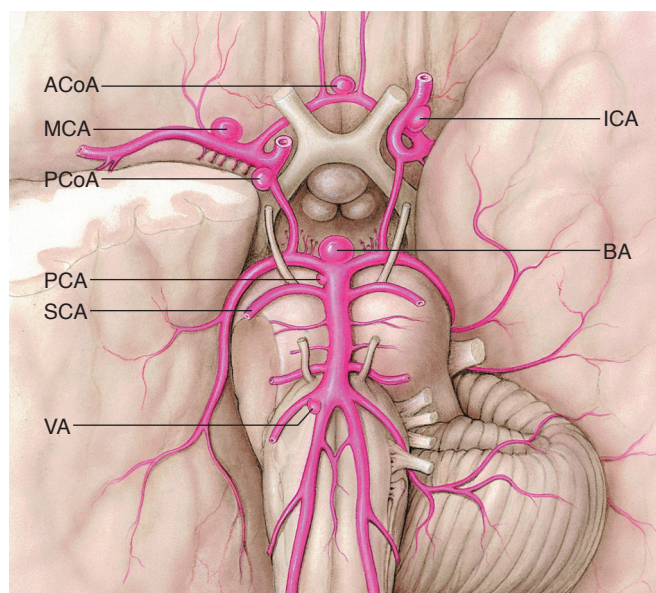


Figure 14-14 Drawing shows locations for intracranial aneurysms arising from cerebral blood vessels. ACoA = anterior communicating artery, BA = basilar artery, ICA = internal carotid artery, MCA = middle cerebral artery, PCA = posterior cerebral artery, PCoA = posterior communicating artery, SCA = superior cerebellar artery, VA = vertebral artery. (Reprinted from Kline LB, Foroozan R, eds. *Optic Nerve Disorders*. 2nd ed. *Ophthalmology Monographs* 10. New York: Oxford University Press, in cooperation with the American Academy of Ophthalmology; 2007:131.)

morbidity and mortality result from aneurysm rupture, early detection and surgical intervention can be life-saving.

Clinical presentation of cerebral aneurysms

Unruptured aneurysms, particularly giant aneurysms, may cause progressive neurologic dysfunction because of their mass effect. An ophthalmic artery aneurysm may cause a progressive unilateral optic neuropathy and ipsilateral periocular pain. Anterior communicating artery aneurysms may cause loss of vision by compressing the optic chiasm or optic tract. Aneurysms at the junction of the internal carotid and posterior communicating arteries cause an ipsilateral CN III palsy. Any complete CN III palsy with pupil involvement and any partial CN III palsy with or without pupil involvement should raise suspicion for an aneurysm and prompt immediate neuroimaging. Diagnostically, pain is not a helpful symptom, because it may occur with CN palsies from microvascular ischemia and may be absent with unruptured aneurysms. TIAs, cerebral infarction, and seizures may be caused by flow phenomena or distal embolization.

Intracavernous carotid artery aneurysms typically produce a cavernous sinus syndrome. These aneurysms are often a fusiform enlargement (dolichoectasia) and not sacular. CNs III, IV, and VI and the ophthalmic branch of CN V are involved, singly or in combination. Because they are confined by the walls of the cavernous sinus, these aneurysms typically do not rupture, instead causing progressive neurologic dysfunction.

Aneurysms in this location often produce facial pain and should be considered in the differential diagnosis of painful ophthalmoplegia.

A ruptured aneurysm is a neurosurgical emergency. Patients exhibit symptoms and signs of subarachnoid or intraparenchymal hemorrhage. The headache resulting from a ruptured aneurysm may be localized or generalized and is often described as “the worst of my life.” Nausea, vomiting, and neck stiffness signify meningeal irritation from subarachnoid blood. In rare cases, fever may be present. Elevated intracranial pressure may produce papilledema and CN VI palsies. Patients may be disoriented, lethargic, or comatose. Altered mental status is a poor prognostic sign.

Ocular hemorrhage may accompany subarachnoid hemorrhage. Intraretinal, preretinal, subhyaloid, vitreous, subconjunctival, orbital, or optic nerve sheath hemorrhage may be present. Ocular hemorrhages are most likely produced when intracranial pressure in the optic nerve sheath exceeds ocular venous pressure, reducing ophthalmic venous drainage and causing venous rupture. The combination of vitreous and subarachnoid hemorrhage is called *Terson syndrome* (Fig 14-15). Many patients recall symptoms of a “sentinel bleed” before the major rupture. Transient or mild neurologic symptoms with headache are most commonly described.

Diagnosis of cerebral aneurysms

Any patient suspected of harboring an aneurysm requires urgent neuroradiologic investigation. The specific type of study ordered varies, and the decision should involve the neuroradiologist (see Chapter 2).

CTA is the imaging modality of choice for diagnosis of clinically relevant aneurysms at most sites. MRI demonstrates most aneurysms larger than 5 mm, and high-quality MRA can detect aneurysms as small as 3 mm. CTA or MRA is useful to screen for unruptured aneurysms; both procedures are less expensive and associated with lower morbidity than conventional angiography (Fig 14-16). However, if there is a high level of suspicion for aneurysm, a negative finding on MRA or CTA does not obviate the need for the “gold standard” evaluation using conventional cerebral arteriography.

CT is useful immediately after aneurysm rupture to detect the presence of intraparenchymal and subarachnoid blood. An enhanced CT scan can demonstrate large aneurysms, but CT alone is not an acceptable screening test for unruptured aneurysms. If subarachnoid hemorrhage is suspected and the CT finding is negative, CTA or lumbar puncture is needed to confirm the presence of subarachnoid blood. However, a lumbar

Figure 14-15 Fundus photograph shows consequences of a ruptured intracranial aneurysm, which may produce hemorrhage within the retina, preretinal space, or vitreous (Terson syndrome). (Courtesy of Steven A. Newman, MD.)



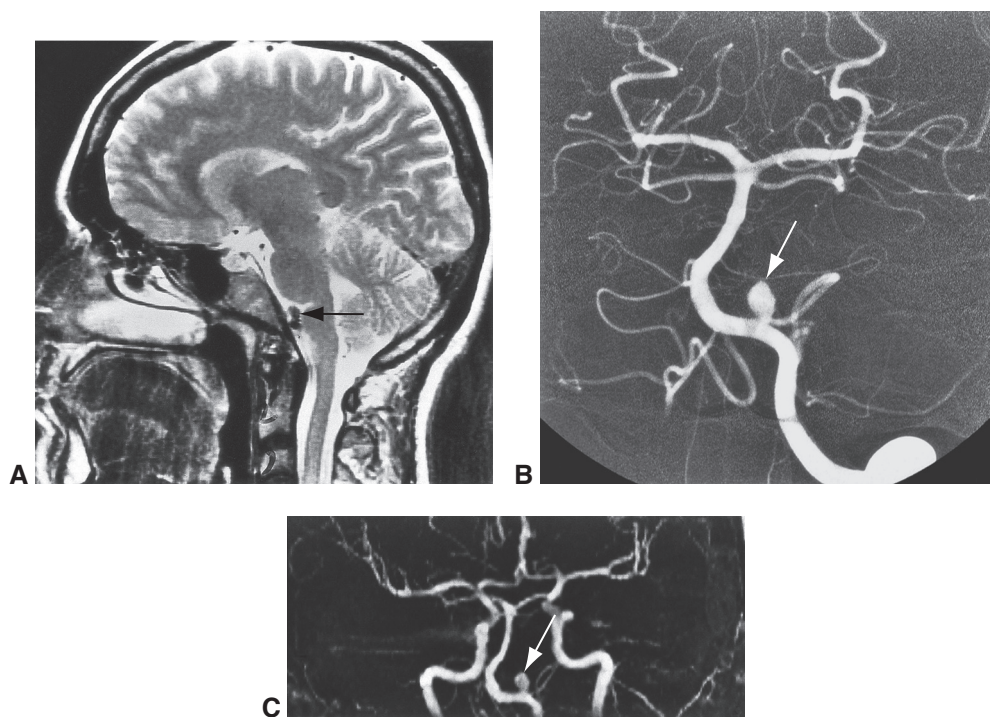


Figure 14-16 Imaging of cerebral aneurysms. **A**, Sagittal view of the brain on a T2-weighted MRI scan shows a low-intensity signal in the subarachnoid space anterior to the medulla (arrow), contiguous with the vertebral artery inferiorly, consistent with flowing blood. **B**, Conventional arteriography shows a vertebral artery aneurysm (arrow). **C**, The same aneurysm, as demonstrated by magnetic resonance angiography (MRA) (arrow). (Courtesy of Leo Hochhauser, MD.)

puncture should not be attempted in the presence of midline shift or evidence of cerebral (uncal) herniation.

Prognosis for patients with cerebral aneurysms

Modern imaging technology (MRA and CTA) has dramatically increased the detection of unruptured intracranial aneurysms. The risk of rupture is related to the size of the aneurysm. Aneurysms that are 7–12 mm, 13–24 mm, and 25 mm or greater have a yearly rupture rate of 1.2%, 3.1%, and 8.6%, respectively. Once an aneurysm has ruptured, morbidity and mortality are high. The proportion of patients who die at the time of rupture is 30%. If untreated, another 33% die within 6 months of rupture, and 15% more die within 10 years. Many of those who survive suffer severe neurologic deficits.

Wiebers DO, Whisnant JP, Huston J III, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003; 362(9378):103–110.

Treatment of cerebral aneurysms

Treatment of symptomatic aneurysms before rupture is ideal and should be performed without delay. Supportive treatment to stabilize the patient includes efforts to lower intracranial pressure (via hyperventilation or administration of mannitol), treat cerebral

vasospasm (with calcium channel blockers and blood volume expansion), control blood pressure, and prevent seizures.

The definitive treatment is surgical clipping of the aneurysm; however, endovascular techniques such as coil embolization or stent placement are replacing clipping as the preferred treatment for many aneurysms, depending on the aneurysm's size, location, and anatomy.

Thompson BG, Brown RD Jr, Amin-Hanjani S, et al. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for the healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015; 46(8):2368–2400.

Arterial Dissection

Dissections may develop in the internal carotid artery (ICA) or in any of its branches, as well as in the vertebral and basilar arteries. Dissection may arise either extracranially or intracranially. Risk factors for a dissection include trauma, cervical manipulation, connective tissue disorders, and fibromuscular dysplasia.

Clinical presentation of arterial dissection

Arterial dissection's clinical features are variable. Patients may incur stroke, which typically occurs within the first 30 days of the dissection. The most common presentation of ICA dissection is acute pain located on the ipsilateral forehead, around the orbit, or in the neck. Other manifestations include ipsilateral ophthalmic signs and contralateral neurologic deficits (see Chapter 10, Fig 10-4). A bruit may be present. Sometimes symptoms of arterial dissection are delayed for weeks or months after trauma. Transient or permanent neurologic symptoms and signs include amaurosis fugax, acute stroke, monocular vision loss, and ipsilateral Horner syndrome. If the dissection extends to the intracranial carotid segment, cranial neuropathies can occur, producing diplopia, dysgeusia, tongue paralysis, or facial numbness.

The vision loss associated with ICA dissection may be a result of embolic occlusion of the ophthalmic artery, central retinal artery, short posterior ciliary arteries, or retinal branch arteries. Alternatively, ophthalmic artery occlusion may be caused by the dissection itself. Reduced blood flow from ICA dissection is a rare cause of ocular ischemic syndrome.

The vertebral and basilar arteries are affected in 40% of dissections. General features of these dissections are headache, neck pain, and signs of brainstem and cerebellar dysfunction. Ocular motor CN palsies are common, and the consequences may progress to include quadriplegia, coma, and death.

Caplan LR, Biousse V. Cervicocranial arterial dissections. *J Neuroophthalmol*. 2004;24(4): 299–305.

Diagnosis of arterial dissection

MRI is the diagnostic test of choice for an extracranial ICA dissection. MRI shows a false lumen or an area of clotting in the cervical portion of the carotid artery (“crescent moon” sign; see Fig 10-4) and may identify areas of brain infarction. CTA or MRI/MRA has a sensitivity of 87%–100%. CTA has the added benefit of allowing visualization of the vertebrobasilar system. Digital subtraction angiography may also be used for diagnosis.

Ultrasonography is not sufficient to detect a carotid dissection and can elicit a false-negative result in nearly one-third of cases.

Treatment of arterial dissection

The treatment of arterial dissection depends on the extent and location of the dissection and the patient's overall condition. Treatment methods may include medical therapy using antiplatelet drugs or anticoagulants, endovascular therapy with stent placement, and, in rare cases, surgery with bypass procedures.

Arteriovenous Malformations

Like aneurysms, AVMs are usually congenital and may be familial. Symptoms typically arise before 30 years of age, with a slight male preponderance, and 6% of patients also have an intracranial aneurysm. Intracranial hemorrhage with or without subarachnoid hemorrhage is the initial presentation in half of the cases. In contrast to patients with saccular aneurysms, patients with AVMs are much more likely to become symptomatic before a hemorrhage occurs (Fig 14-17). Seizures are the first manifestation in 30% of affected patients, whereas 20% have headaches or other focal neurologic deficits initially. The neurologic symptoms may be progressive or transient.

Of the 90% of AVMs that are supratentorial, about 70% are cortical and 20% are deep. The remaining 10% of AVMs are located in the posterior fossa or dura mater. Early mortality occurs in up to 20% of cases when bleeding takes place, and the rebleeding rate is 2.5% each year. Most AVMs bleed into the brain, causing headaches and focal neurologic deficits.

An AVM's neuro-ophthalmic manifestations depend on its location. Cortical AVMs in the occipital lobe may produce visual symptoms and headaches that resemble migraine. The visual phenomena are usually brief and unformed; typical migrainous scintillating scotomata may occur but are rare (see Chapter 12, Fig 12-1). Hemispheric AVMs may produce homonymous visual field defects. Signs and symptoms of brainstem AVMs are not specific and may include diplopia, nystagmus, dizziness, ocular motor nerve palsy, gaze palsy, anisocoria, or pupillary light–near dissociation. Reports of transient monocular visual loss caused by a steal phenomenon from an intracranial AVM are rare.

Some patients with AVMs report a subjective intracranial bruit, and occasionally the examiner will detect a bruit via auscultation of the skull over the AVM.

Abnormal arterial communication with one of the dural venous sinuses (dural AVM) results in elevated venous pressure and, in turn, increased intracranial pressure. Dural AVMs account for 10%–15% of intracranial AVMs. Patients often have tinnitus and an audible bruit in addition to signs and symptoms of increased intracranial pressure. Dural AVMs are difficult to diagnose without catheter angiography and may be mistaken for typical IIH (see Chapter 4). Dural AVMs should be considered if the patient does not fit the usual IIH demographics and has no other demonstrable cause of increased intracranial pressure.

Diagnosis of arteriovenous malformations

If bleeding is suspected, an unenhanced CT scan will show the hemorrhage. Although unruptured AVMs are typically apparent on an enhanced CT scan, MRI is more sensitive

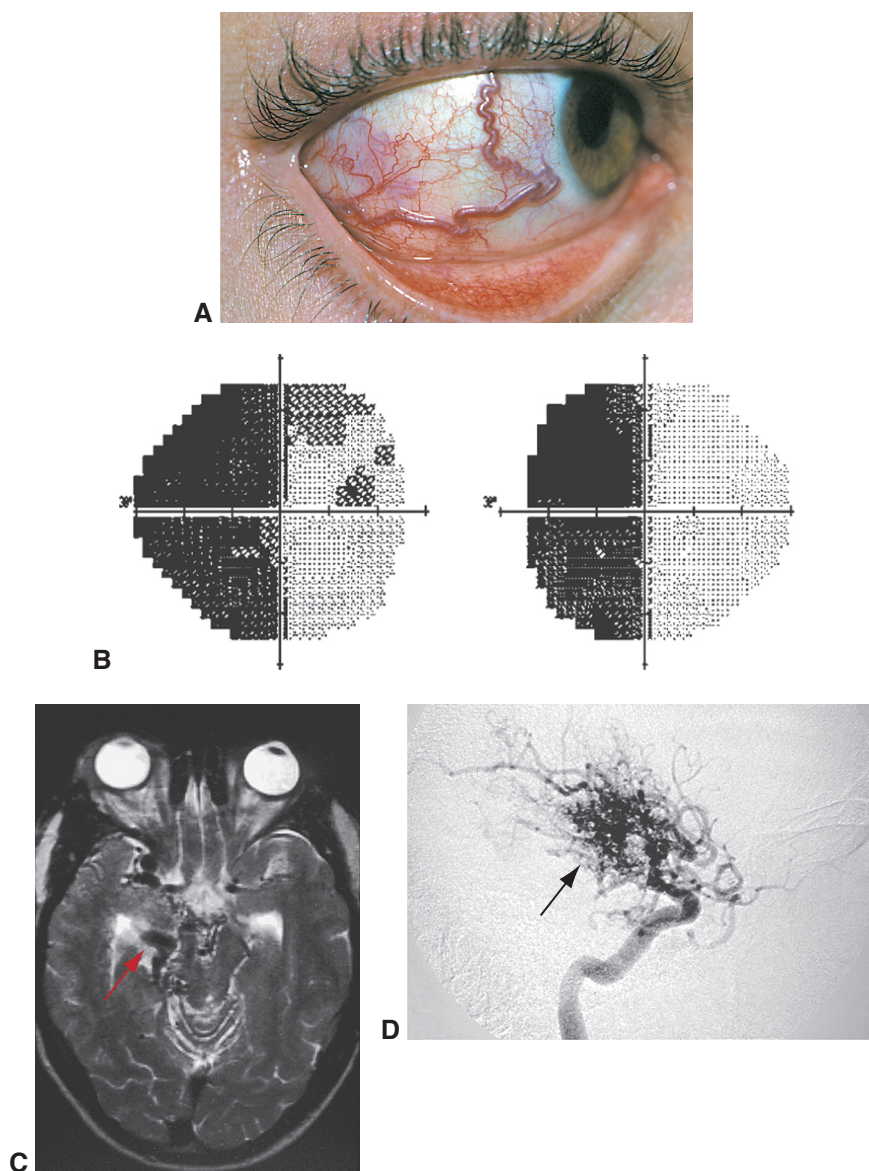


Figure 14-17 Arteriovenous malformation (AVM). **A**, This 24-year-old man was referred with a 2- to 3-year history of prominent blood vessels in the right eye. Visual acuity was 20/20 bilaterally, but visual fields (**B**) demonstrated a left homonymous hemianopia. **C**, AT2-weighted MRI scan demonstrated a large right basal ganglia AVM (red arrow). **D**, Angiogram of the right internal carotid artery confirmed the basal ganglia AVM (arrow). (Courtesy of Steven A. Newman, MD.)

for visualizing small AVMs. MRI demonstrates the heterogeneous signals representing the various elements of the lesion: blood vessels, brain, flowing and clotted blood, calcium, hemorrhage, or edema. Calcified AVMs are sometimes identifiable on plain radiograph or CT scan. Cerebral angiography is required to show the anatomy clearly and to define the feeding and draining vessels of the AVM.

Treatment of arteriovenous malformations

The location of the AVM, the anatomy of the feeding and draining vessels, and the size of the lesion all affect the choice of treatment. The treatment modalities, including surgical resection, ligation of feeding vessels, embolization, and stereotactic radiosurgery, can be used alone or in combination. Seizures usually improve with anticonvulsant therapy.

Crimmins M, Gobin YP, Patsalides A, Knopman J. Therapeutic management of cerebral arteriovenous malformations: a review. *Expert Rev Neurother*. 2015;15(12):1433–1444.

Cerebral Venous Thrombosis

Occlusion of the cortical and subcortical veins causes focal neurologic symptoms and signs, including neuro-ophthalmic findings. Most commonly affected are the cavernous sinus, lateral (transverse) sinus, and superior sagittal sinus; each produces a distinct clinical syndrome. During pregnancy, the lateral and superior sagittal sinuses are more commonly affected. Patients with thrombosis may present with headaches and papilledema, and the thrombosis could be confused with IIH. Thrombosis of the deep veins may cause infarction of the thalamus or basal ganglia, and death can occur in 3%–15% of cases.

Types of cerebral venous thrombosis

Cavernous sinus thrombosis Cavernous sinus thrombosis (CST) in the *septic* form results from an infection of the face, oral cavity, or sphenoid or ethmoidal sinuses. Otitis media or orbital cellulitis is a rare cause. Patients experience headache, nausea, vomiting, and somnolence. There may also be fever, chills, tachycardia, evidence of meningitis, or generalized sepsis. Ocular signs from anterior infection (facial, dental, or orbital) are initially unilateral but frequently become bilateral. These signs include orbital congestion, lacrimation, conjunctival edema, eyelid swelling, ptosis, proptosis, and ophthalmoplegia. CN VI palsy is the most consistent early neurologic sign. Corneal anesthesia, facial numbness, Horner syndrome, and venous stasis retinopathy can occur. Septic CST is a medical emergency; it carries a high mortality rate if it is not recognized promptly and if treatment is not initiated immediately. The mainstay of therapy is early and aggressive antibiotic administration. Anticoagulation is often recommended as adjunctive therapy. Corticosteroids may help to reduce inflammation and edema. If feasible, the primary source of infection should be drained.

The signs and symptoms of *aseptic* CST resemble those of septic CST, but clinical or laboratory examination shows no evidence of infection. Pain around the eye is common, but orbital congestion is typically less severe than with septic CST. Anticoagulation or antiplatelet therapy is often used.

Lateral (transverse) sinus thrombosis Lateral sinus thrombosis may be septic or spontaneous (see Chapter 2, Fig 2-13). With the widespread use of antibiotics, septic thrombosis has become rare, but it may result from otitis media.

Patients with lateral sinus thrombosis have features of systemic infection as well as neck pain, tenderness of the ipsilateral jugular vein, retroauricular edema, and sometimes, facial weakness. Severe facial pain also may occur; when accompanied by CN VI palsy it is called *Gradenigo syndrome*. Lateral sinus thrombosis is much more likely to be

spontaneous and produce an IIH-like syndrome with increased intracranial pressure. The most common ophthalmic signs are papilledema and CN VI palsy.

Superior sagittal sinus thrombosis The most commonly involved cerebral venous sinus is the superior sagittal sinus (SSS); symptoms of its thrombosis depend on the extent and location of the occlusion. With thrombosis of the anterior third of the sinus, symptoms are mild or absent. Posterior SSS thrombosis may produce a clinical picture similar to that of IIH, with headaches and papilledema. It is a diagnosis to consider in atypical IIH patients, such as slim women and men. Seizures and motor deficits may occur.

Diagnosis of cerebral venous thrombosis

Neuroimaging is required to diagnose CVT. CT or MRI is often used initially, but a targeted venographic study, such as magnetic resonance venography (MRV) or computed tomography venography (CTV) should also be considered. Cerebral venography may be used in cases in which clinical suspicion is high despite normal CTV or MRV findings.

Laboratory evaluation of cerebral venous thrombosis

Prothrombotic conditions are present in 21%–34% of patients with CVT, most commonly protein C deficiency, protein S deficiency, presence of antiphospholipid and anti-cardiolipin antibodies, factor V Leiden, presence of prothrombin G20210A mutation, and hyperhomocysteinemia. Other predisposing factors include pregnancy, use of oral contraceptives, and systemic conditions including cancer, facial infections, inflammatory diseases, and hematologic diseases.

Treatment of cerebral venous thrombosis

Treatment of CVT is directed toward the underlying condition. Therapies include use of anticoagulants, fibrinolytic drugs, and treatments to lower intracranial pressure. Antiepileptic drugs are used for patients with seizures. Corticosteroids are typically not used in CVT treatment unless required for management of the underlying inflammatory disease. Endovascular interventional therapy using modern approaches to intracranial recanalization may be needed in symptomatic patients showing resistance to medical treatment.

Patients with CVT may benefit from receiving care in a dedicated hospital stroke unit to ensure adequate treatment and to prevent complications.

Bushnell C, Saposnik G. Evaluation and management of cerebral venous thrombosis. *Continuum (Minneapolis)*. 2014;20(2):335–351.

Mokin M, Lopes DK, Binning MJ, et al. Endovascular treatment of cerebral venous thrombosis: contemporary multicenter experience. *Interv Neuroradiol*. 2015;21(4):520–526.

Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe recurrent headaches (“thunderclap headaches”) with or without focal neurologic deficits and/or seizures as well as segmental constriction of cerebral arteries that resolves within 3 months. Visual complaints are frequent and include light sensitivity, blurred vision, and hemianopic visual field loss. This syndrome mainly affects middle-aged women, and more than one-half of RCVS cases occur during the postpartum period or after exposure to

vasoactive substances (eg, selective serotonin reuptake inhibitors, triptans, amphetamines, ergotamine, nasal decongestants, or cannabis). Although the syndrome may be self-limited and benign, it may lead to ischemic stroke or nonaneurysmal subarachnoid hemorrhage. MRA or conventional angiography may demonstrate the characteristic “string-of-beads” appearance of the cerebral arteries. Calcium channel blockers are the standard therapies, but these have no proven effect on the syndrome’s hemorrhagic and ischemic complications (Fig 14-18).

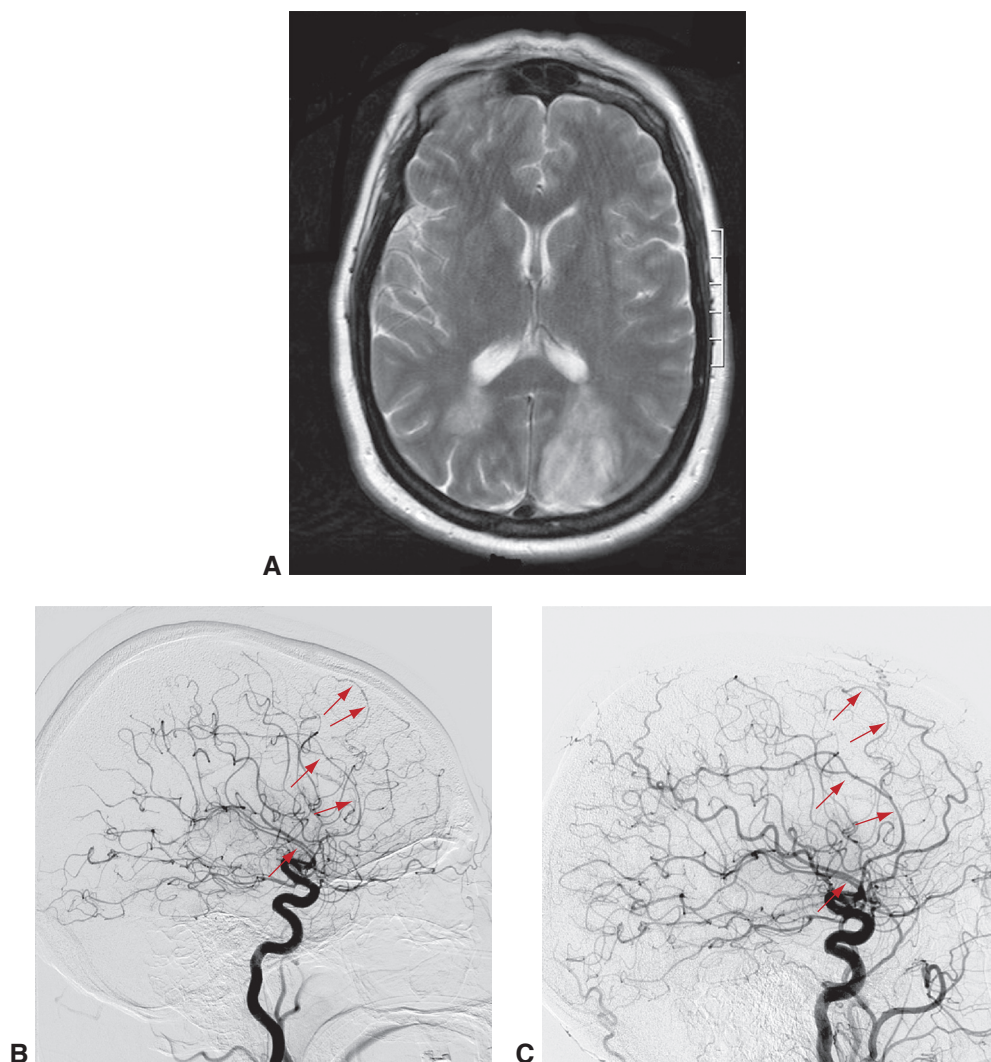


Figure 14-18 Reversible cerebral vasoconstriction syndrome (RCVS) in a 34-year-old woman presenting with headache and a right homonymous hemianopia. **A**, Axial T2-weighted brain MRI shows a bilateral occipital infarct greater on the left than the right. **B**, Cerebral angiogram demonstrates multiple areas of segmental arterial narrowing (*arrows*). **C**, Areas of intracerebral vasoconstriction quickly improved 5 minutes after treatment with intravenous verapamil (*arrows*). (Courtesy of Hormozd Bozorgchami, MD.)

Raven ML, Ringeisen AL, McAllister AR, Knoch DW. Reversible cerebral vasoconstriction syndrome presenting with visual field defects. *J Neuroophthalmol.* 2016;36(2):187–190.

Neuro-Ophthalmic Manifestations of Infectious Diseases

Myriad infectious diseases may result in neuro-ophthalmic manifestations. This text covers the most common infections that produce neuro-ophthalmic symptoms and occur in the United States.

Human Immunodeficiency Virus Infection

Neuro-ophthalmic disorders associated with human immunodeficiency virus (HIV) infection may result either from direct infection or from indirect causes such as secondary opportunistic infections, malignancy, microvasculopathy, or uveitis. The eye, afferent visual pathways, and ocular motor system can all be affected. BCSC Section 9, *Uveitis and Ocular Inflammation*, discusses the following conditions in detail.

Human immunodeficiency virus

HIV infection causes acute and chronic CNS manifestations. Acute aseptic meningitis and meningoencephalitis affect 5%–10% of patients, soon after initial HIV infection. Headache, fever, and meningeal signs may accompany a mononucleosis-like syndrome. Occasionally, altered mental status, seizures, optic neuropathy, and cranial neuropathies occur, most commonly CN VII paresis.

HIV encephalopathy, also known as the *AIDS dementia complex* or *HIV-associated neurocognitive disorder*, begins with impaired memory and concentration, behavior changes, and mental slowness. Abnormal pursuit, saccadic eye movements, and saccadic intrusions (square-wave jerks) may be present. Late manifestations include profound dementia, behavior changes, psychosis, psychomotor impairment, weakness, visual neglect, visual hallucinations, seizures, and tremor. An optic neuropathy may develop. MRI demonstrates cerebral atrophy and areas of white matter hyperintensity on T2-weighted images that correspond to areas of demyelination produced by the virus.

Ocular signs of HIV infection include cotton-wool spots, perivasculitis, and retinal hemorrhages. Subtle structural and functional retinal and optic nerve abnormalities, termed *HIV-associated neuroretinal disorder (HIV-NRD)*, have been reported in HIV-infected patients without infectious retinitis or any apparent funduscopic abnormalities. Risk factors for this disorder include low CD4⁺ T cell counts, detectable HIV RNA in the blood, and hepatitis C infection. Patients with HIV-NRD may demonstrate thinner retinal nerve fiber layer, subtle loss of color vision and/or contrast sensitivity, visual field deficits, and subnormal electrophysiologic responses. Studies found that HIV-NRD is associated with increased mortality and increased risk of bilateral visual impairment. Antiretroviral therapy decreases but does not eliminate the risk of HIV-NRD.

Jabs DA, Drye L, Van Natta ML, Thorne JE, Holland GN; Studies of the Ocular Complications of AIDS Research Group. Incidence and long-term outcomes of the human immunodeficiency virus neuroretinal disorder in patients with AIDS. *Ophthalmology.* 2015;122(4):760–768.

Central nervous system lymphoma

After Kaposi sarcoma, which is the most common AIDS-associated neoplasia of the eyelid or conjunctiva, high-grade B-cell non-Hodgkin lymphoma is the second most common malignancy in patients with AIDS and the most common neoplasm to affect the CNS. CNS lymphoma can cause diplopia from CN III, IV, or VI involvement. Lymphomatous infiltration of the orbit and optic nerve may lead to ONH swelling and vision loss. The diagnosis is made by confirming the presence of neoplastic lymphomatous cells in the CSF or through results of stereotactic brain or meningeal biopsy. Changes shown on MRI scan may resemble those of toxoplasmosis, but they are typically periventricular with subependymal spread. Treatment consists of a combination of radiotherapy and chemotherapy.

Cytomegalovirus

Cytomegalovirus (CMV) infection is a common opportunistic infection and a major cause of vision loss in HIV-infected patients. CMV retinitis is often the presenting manifestation of untreated advanced HIV infection and primarily occurs in patients with extremely low CD4⁺ T-lymphocyte cell counts. Within the CNS, CMV infection causes optic neuritis and brainstem encephalitis. Anterior optic nerve infection produces acute loss of vision with ONH swelling; this condition usually occurs in patients with severe CMV retinitis. Other patients exhibit anterior optic neuropathy with minimal retinitis (Fig 14-19). Posterior optic neuropathy, which is rare, is characterized by slowly progressive loss of vision without ONH edema. Brainstem involvement may cause ptosis, internuclear ophthalmoplegia, ocular motor CN palsies, horizontal and vertical gaze paresis, and nystagmus.

The diagnosis of CMV infection is made clinically, based on the characteristic ocular findings. Results of serologic tests and cultures may indicate elevations or be inconclusive. Polymerase chain reaction diagnostic testing of CSF may be an important molecular tool. See BCSC Section 9, *Uveitis and Ocular Inflammation*, for a complete discussion of CMV diagnosis and treatment.

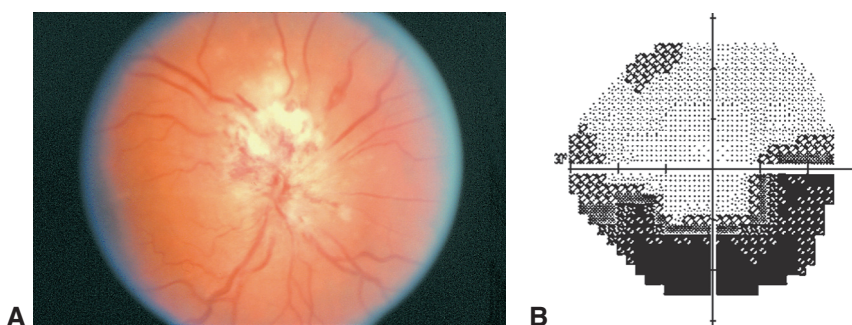


Figure 14-19 Cytomegalovirus (CMV) optic neuritis. **A**, Fundus photograph shows optic nerve head (ONH) appearance of a 42-year-old woman who presented 3 weeks after noticing inferior shadows in the right eye. Visual acuity was 20/20, but visual field testing (**B**) demonstrated an inferior arcuate visual field defect. The patient's medical history was remarkable for transfusion 18 months prior, with evidence of subsequent *Pneumocystis jiroveci* pneumonia. She was found to be HIV-seropositive, and a diagnosis of CMV optic neuritis was made. (Courtesy of Steven A. Newman, MD.)

Butler NJ, Thorne JE. Current status of HIV infection and ocular disease. *Curr Opin Ophthalmol.* 2012;23(6):517–522.

Herpesvirus

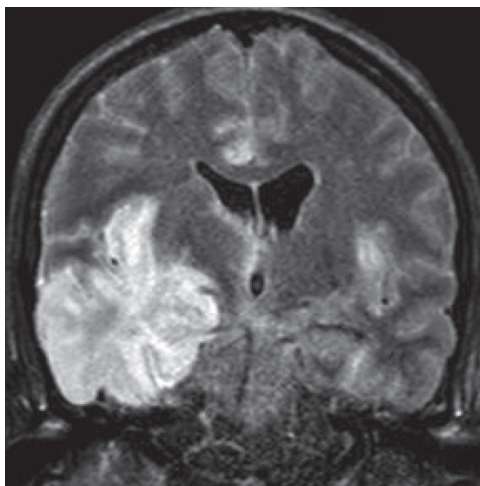
Herpes simplex virus (human herpesvirus 1 and 2) and herpes varicella-zoster virus can cause acute outer retinal necrosis, resulting in photophobia, ocular pain, floaters, and decreased visual acuity. Ophthalmic findings include panuveitis, vitritis, retinal arteritis, ONH edema, and a necrotizing retinitis that initially spares the posterior pole. See BCSC Section 9, *Uveitis and Ocular Inflammation*.

The most common neurologic manifestation of herpes infection is CNS encephalitis (Fig 14-20). Radiculitis may occur, producing Ramsay Hunt syndrome (see Chapter 11) and herpes zoster ophthalmicus (HZO). Neuro-ophthalmic complications of HZO include ischemic optic neuropathy, optic neuritis, and ocular motor CN palsy. In the majority of cases, HZO-induced ophthalmoplegia occurs within 2 weeks of onset of the HZO rash. Treatment with oral antiviral therapy and oral corticosteroids is usually recommended. This self-limiting ophthalmoplegia improves over the course of several months; the majority of patients recover from the diplopia, at least in primary gaze.

Mycobacterium

Mycobacterium tuberculosis and *Mycobacterium avium-intracellulare* complex can infect the brain and eye. The neuro-ophthalmic manifestations of tuberculous meningitis include photophobia, CN III and VI paresis, papilledema, retrobulbar optic neuritis, and anisocoria. Cerebral infarction can result from obliterative endarteritis. Neuroimaging studies may show hydrocephalus, abscess formation, granulomas, and enhancement of the basal meninges with contrast administration. Ethambutol is used along with other medications to treat mycobacterial infection; toxicity from this medication can cause bilateral, progressive, painless vision loss (see Chapter 4).

Figure 14-20 Coronal FLAIR MRI scan shows signal abnormalities mainly affecting the temporal lobes (much greater on the right than the left) in a patient with herpes encephalitis. (Courtesy of Bronwyn Hamilton, MD.)



Syphilis

Syphilis is a multisystem, chronic bacterial disease caused by the spirochete *Treponema pallidum*. Syphilis has been associated with numerous ophthalmic and neurologic manifestations. This condition can be resolved with appropriate antimicrobial therapy, but delay in the diagnosis can lead to significant ocular and neurological morbidity. See BCSC Section 9, *Uveitis and Ocular Inflammation*, for an extensive review of syphilis.

Progressive Multifocal Leukoencephalopathy

Originally described in patients with lymphoproliferative disorders and impaired cell-mediated immunity, PML occurs in 1%–4% of HIV-infected patients. PML has also been reported in patients with MS who have been treated with immunomodulating medications such as natalizumab. The disease is caused by the JC virus, a polyomavirus that infects oligodendrocytes. Gray matter is relatively spared. The central visual pathways and ocular motor fibers can be affected. Neuro-ophthalmic manifestations include homonymous hemianopia, blurred vision, cerebral blindness, prosopagnosia, and diplopia. Other neurologic findings are altered mental status, ataxia, dementia, hemiparesis, and focal deficits. Behavioral and cognitive abnormalities are very common.

MRI scan shows areas of demyelination, most frequently in the parieto-occipital region. PML typically involves the subcortical white matter, with focal or confluent nonenhancing lesions (Fig 14-21). Therapy is aimed at correcting the underlying

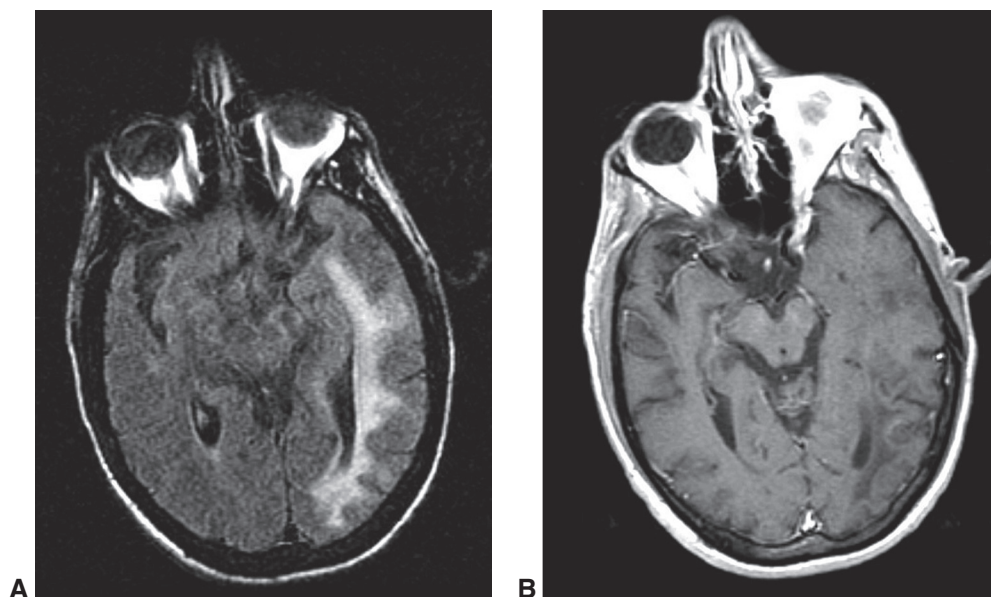


Figure 14-21 Progressive multifocal leukoencephalopathy (PML) in a patient with AIDS. **A**, Axial FLAIR image demonstrates increased signal in the left occipital lobe white matter that extends anteriorly. **B**, Axial gadolinium-enhanced T1-weighted spin-echo image (same location as part **A**) demonstrates a nonenhancing hypointense lesion in the left occipital white matter. T1 hypointensity is typical of PML lesions. Note the absence of mass effect and negligible enhancement. (Courtesy of Joel Curé, MD.)

immune deficiency state, and prognosis is poor. In some cases, plasma exchange may be helpful.

Sørensen PS, Bertolotto A, Edan G, et al. Risk stratification for progressive multifocal leukoencephalopathy in patients treated with natalizumab. *Mult Scler.* 2012;18(2):143–152.

Sudhakar P, Bachman DM, Mark AS, Berger JR, Kedar S. Progressive multifocal leukoencephalopathy: recent advances and a neuro-ophthalmological review. *J Neuroophthalmol.* 2015;35(3):296–305.

Toxoplasmosis

Toxoplasmosis is the most common cause of infectious posterior uveitis in adults and children. The ocular manifestations, which are common, are extensively discussed in BCSC Section 9, *Uveitis and Ocular Inflammation*.

CNS toxoplasmosis is often associated with immune deficiency. Toxoplasmic optic neuritis is rare, characterized by subacute visual loss and ONH swelling, at times accompanied by a macular star (neuroretinitis). CNS toxoplasmosis produces multifocal lesions, with a predilection for the basal ganglia and the frontal, parietal, and occipital lobes. Patients experience headaches, focal neurologic deficits, seizures, mental status changes, and fever. Neuro-ophthalmic findings include homonymous hemianopia and quadrantanopia, ocular motor CN palsies, and gaze palsies. Long-term antitoxoplasmosis treatment is necessary to prevent recurrences.

MRI typically shows multiple lesions that are isointense with the brain on T1-weighted images and isointense or hyperintense on T2-weighted images. Gadolinium administration reveals enhancement.

Lyme Disease

Lyme borreliosis is caused by infection with *Borrelia burgdorferi*, a spirochete transmitted by deer ticks. The disease, which typically occurs in 3 stages, can produce ocular and neuro-ophthalmic manifestations. Lyme disease is discussed further in BCSC Section 1, *Update on General Medicine*, and Section 9, *Uveitis and Ocular Inflammation*.

Along with various uveitic entities, neuro-ophthalmic findings occur primarily in *stage 2* and include papilledema (IIH-like syndrome), optic neuritis, papillitis, neuroretinitis, and orbital myositis. Two-thirds of patients have ocular findings at this stage. Cranial neuropathies can occur, most commonly CN VII palsy, as well as radiculopathies and meningitis with headache and neck stiffness.

In *stage 3*, neurologic conditions (neuroborreliosis) predominate, including chronic encephalomyelitis, spastic paraparesis, ataxic gait, subtle mental disorders, and chronic radiculopathy. The neurologic picture may resemble that of MS, clinically and radiographically. In rare instances, Lyme can cause repeat cerebrovascular events in multiple locations within short time intervals.

The diagnosis is made clinically when the patient has been exposed to an endemic area (the patient might not recall a tick bite) and shows the typical rash of erythema chronicum migrans (Fig 14-22). The presence of an elevated Lyme antibody titer in the serum or CSF



Figure 14-22 Erythema chronicum migrans, the characteristic skin rash of stage 1 Lyme disease. (Courtesy of Robert L. Lesser, MD.)

is helpful. The enzyme-linked immunosorbent assay (ELISA) is typically used for screening, but a positive result using the Western blot technique confirms the diagnosis.

Treatment should be orchestrated by a specialist in infectious diseases.

Träisk F, Lindquist L. Optic nerve involvement in Lyme disease. *Curr Opin Ophthalmol.* 2012;23(6):485–490.

Fungal Infections

The 2 main types of fungi are molds and yeasts, although some fungi can have characteristics of both. Molds (filamentous fungi) are composed of hyphae, which extend and branch to form a mycelium, enabling the mold to grow. Molds reproduce when a portion of the hyphae breaks off. Aspergillosis and mucormycosis are CNS infections caused by molds. Yeasts are round, with outpouchings called buds or pseudohyphae. They are septated and reproduce by budding: the parent cell divides and one of the daughter nuclei migrates into a bud on the surface of a cell. Coccidioidomycosis, cryptococcosis, and histoplasmosis are caused by yeasts. *Candida* can grow as a yeast or a mold.

Aspergillosis

The most frequent mode of transmission of *Aspergillus* species is inhalation of spores. The 3 main types of infections are allergic aspergillosis, aspergillomas, and invasive aspergillosis. Allergic aspergillosis affects the bronchopulmonary system and the paranasal sinuses. Allergic *Aspergillus* sinusitis occurs in immunocompetent patients with chronic sinusitis and nasal polyposis. It can invade the orbit, especially with sphenoid sinus involvement, and can result in secondary optic neuropathy, proptosis, diplopia, and retrobulbar pain. Aspergillomas, or fungus balls, may arise in the orbit, paranasal sinuses, or brain. They can occur in either immunocompromised or immunocompetent patients. Orbital aspergillomas produce symptoms of orbital masses, with proptosis, vision loss, diplopia, and pain. Orbital lesions also typically involve the sinuses or brain. Extension to the optic canal, cavernous sinus, optic nerves, and optic chiasm produces neuro-ophthalmic findings (Fig 14-23). Intracranial aspergillomas act like mass lesions, causing progressive neurologic deficits.

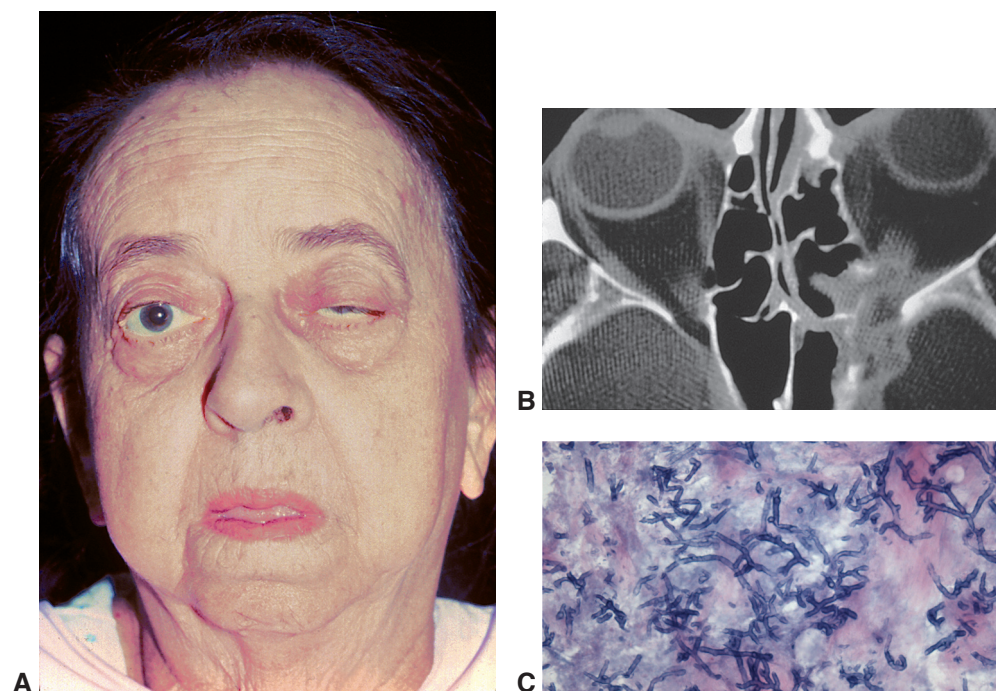


Figure 14-23 This 82-year-old woman presented with a 6-week history of left brow and orbital pain. **A**, 4 weeks before evaluation, she suddenly lost vision in her left eye, and ptosis and proptosis developed 1 week later. **B**, CT scan revealed a destructive lesion at the orbital apex. **C**, Biopsy of the lesion showed septate hyphae consistent with aspergillosis. (Part C courtesy of Julie Falardeau, MD.)

Invasive aspergillosis typically occurs in immunocompromised patients; however, the disease can also affect immunocompetent patients. Most patients initially have pulmonary involvement, although the skin, orbit, or sinuses may be the nidus of infection. CNS infection occurs secondarily by either direct or hematogenous spread of organisms. Ophthalmic manifestations include acute retrobulbar optic neuropathy, endophthalmitis, orbital apex syndrome, and cavernous sinus syndrome. The presentation of invasive aspergillosis is highly variable and can mimic malignancy, idiopathic orbital inflammatory syndrome, GCA, and bacterial cellulitis. Vascular invasion produces cerebral infarction or hemorrhage. Meningitis, intracranial abscess, epidural and subdural hematoma, mycotic aneurysm formation, and encephalitis are serious sequelae of invasive aspergillosis.

Treatment includes antifungal agents such as voriconazole, itraconazole, or posaconazole. Voriconazole may be associated with transient visual disturbances. Surgical intervention is often necessary to treat aspergillomas and invasive aspergillosis. The mortality rate for invasive aspergillosis varies from 40%–80%, depending on predisposing risk factors.

Thurtell MJ, Chiu AL, Goold LA, et al. Neuro-ophthalmology of invasive fungal sinusitis: 14 consecutive patients and a review of the literature. *Clin Experiment Ophthalmol*. 2013; 41(6):567–576.

Zygomycosis

Zygomycetes (genera *Mucor* or *Rhizopus*) are ubiquitous organisms that typically have low virulence, except in debilitated hosts. The mold enters the body through the respiratory tract and proliferates, causing hyphal invasion of tissues. It grows rapidly, producing a more acute infection than other fungi. These organisms have a predilection for blood vessels; hemorrhage, thrombosis, and ischemic necrosis are hallmarks of the disease. Aneurysm and pseudoaneurysm formation in the intracranial vasculature can produce devastating consequences when rupture occurs. The 2 types of zygomycosis (also known as *mucormycosis* or *phycomycosis*) that result in ophthalmic involvement are rhinocerebral zygomycosis and CNS zygomycosis.

Rhinocerebral zygomycosis usually occurs in patients with diabetes mellitus, patients taking corticosteroids, or neutropenic patients receiving antibiotics. The initial infection spreads from the facial skin, nasal mucosa, paranasal sinuses, or hard palate (Fig 14-24). The fungus spreads to the nearby blood vessels, affecting the orbital vessels, carotid arteries, cavernous sinuses, or jugular veins. Orbital and neurologic signs are produced by infarction, thrombosis, or hemorrhage. If untreated, rhinocerebral zygomycosis may bring about rapid deterioration, leading to death within days. A few patients may have a chronic course with little indication of systemic illness. The most common signs and symptoms include fever, nasal necrosis, periorbital swelling, decreased vision, ophthalmoplegia, sinusitis, and headache. Retinal infarction, ophthalmic artery occlusion, and optic nerve infiltration are mechanisms of blindness. Neurologic signs include hemiparesis, aphasia, seizures, and altered mental status.

CNS zygomycosis is very rare. The fungus usually gains access into the CNS from the nose or paranasal sinus, but there is no nasal, sinus, ocular, or orbital disease when the neurologic manifestations appear. Infection of the orbit, palate, nose, and sinuses typically occurs secondarily. Meningitis, abscesses, CN involvement, and seizures are common.

The diagnosis of zygomycosis requires a high index of suspicion. CT scan may demonstrate bone destruction, soft-tissue alteration in the paranasal sinuses and orbit, air-fluid levels in the sinuses and orbits, or brain abscess formation. MRI, MRA, and

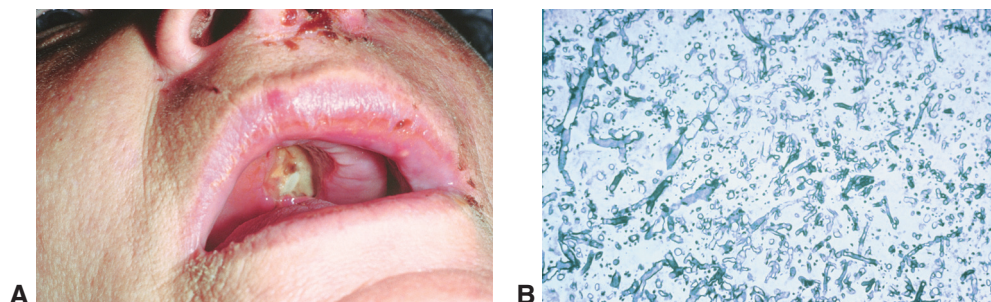


Figure 14-24 Rhinocerebral zygomycosis. **A**, A patient with rhinocerebral zygomycosis eroding the hard palate. **B**, Biopsy specimen demonstrates typical nonseptate hyphae. (Courtesy of Lanning B. Kline, MD.)

arteriography may be helpful for demonstrating vascular thrombosis. The definitive test is a biopsy specimen that demonstrates vascular invasion, tissue necrosis, eschar formation, inflammatory cells, and nonseptate hyphae (by histologic examination).

Zygomycosis has a high mortality rate, although prompt diagnosis and aggressive therapy may be life-saving. The underlying systemic disease should be treated and immunosuppressant agents eliminated, if possible. Therapy includes aggressive surgical debridement of necrotic tissue and administration of antifungal agents both locally and systemically. Hyperbaric oxygen has been used as adjuvant therapy.

Gamaletsou MN, Sipsas NV, Roilides E, Walsh TJ. Rhino-orbital-cerebral mucormycosis.

Curr Infect Dis Rep. 2012;14(4):423–434.

Trief D, Gray ST, Jakobiec FA, et al. Invasive fungal disease of the sinus and orbit: a

comparison between mucormycosis and *Aspergillus*. *Br J Ophthalmol.* 2016;100(2):

184–188.

Cryptococcosis

Cryptococcosis is a fungal disease caused mainly by *Cryptococcus neoformans* and *Cryptococcus gattii*. Inhalation of these fungi and subsequent pulmonary infection may spread to the CNS, causing meningitis or meningoencephalitis. Although *C neoformans*, which is found in pigeon droppings and contaminated soil, is ubiquitous, it rarely causes infection in otherwise healthy people. Affected individuals are typically immunocompromised, predominantly patients with HIV infection or AIDS. *C gattii* typically grows in soil around various kinds of trees; it can produce severe meningoencephalitis as well as pulmonary disease in immunocompromised or immunocompetent individuals.

The most common neuro-ophthalmic abnormality is papilledema from cryptococcal meningitis. Retrobulbar optic neuritis may also be present with gradual loss of vision over hours to days. Other ophthalmic complications include retinochoroiditis and cotton-wool spots. Cranial neuropathies may be observed, including unilateral or bilateral CN VI palsies. Photophobia, blurred vision, retrobulbar pain, homonymous visual field defects, or nystagmus may occur. The onset of symptoms is usually insidious, with a waxing and waning course. Headache, nausea, vomiting, dizziness, and mental status changes are the most common complaints.

The diagnosis is confirmed by isolating the yeast in the CSF or by demonstrating the capsular antigen for *C neoformans* or *C gattii*. In most patients with CNS cryptococcosis the disease is disseminated; there is evidence of infection in the blood, lungs, bone marrow, skin, kidneys, and other organs. Serum antigen titers are helpful for this reason.

Antifungal treatment should be initiated urgently, and aggressive management of intracranial hypertension is often needed. Vision loss caused by papilledema may be treated with CSF shunting or optic nerve sheath fenestration. The mortality rate of patients with treated CNS cryptococcosis is 25%–30%. The prognosis is worse in patients with an underlying malignancy or AIDS.

Franco-Paredes C, Womack T, Bohlmeier T, et al. Management of *Cryptococcus gattii*

meningoencephalitis. *Lancet Infect Dis.* 2015;15(3):348–355.

Prion Diseases

Prion diseases, also known as *transmissible spongiform encephalopathies*, include kuru in New Guinea; sporadic Creutzfeldt-Jakob disease (sCJD), which is found worldwide; familial CJD (fCJD); and variant CJD (vCJD), which is found mostly in the United Kingdom and France. Variant CJD has been linked to bovine spongiform encephalopathy (“mad cow” disease), which is a prion disease in cattle. Other rare types of prion diseases include fatal insomnia (a rare hereditary disorder that causes difficulty sleeping) and Gerstmann-Sträussler-Scheinker syndrome (an extremely rare disorder that typically occurs around age 40).

Prions are infectious agents formed by the conversion of a normal cell surface protein (PrP^C) to a misfolded cell surface protein called PrP^{CJD} or PrP^{SC} (“SC” stands for the animal prion disease scrapie). sCJD may result from somatic mutation in the prion protein gene or, more likely, from the spontaneous, random conversion of a normal prion protein to an abnormal prion protein and the subsequent expansion of the altered form. About 10% of CJD cases are familial, resulting from inherited mutations in the *PrP* gene.

CJD is uniformly fatal, presenting as a rapidly progressive dementia culminating in death, usually within 8 months. The most commonly reported visual manifestations include diplopia, supranuclear palsies, complex visual disturbances, homonymous visual field defects, hallucinations, and cortical blindness. In the Heidenhain variant of CJD, patients present primarily with isolated visual symptoms. Due to the complex clinical manifestations, this rare but clinically distinct group of patients with sCJD may be a diagnostic dilemma. Diffusion-weighted and FLAIR MRI may reveal early cortical changes and PET scan may reveal hypometabolism in posterior cortical regions.

Diagnostic testing for prion disease includes MRI, electroencephalogram (EEG), lumbar puncture, and possibly brain biopsy. Diffusion-weighted MRI images show typical high-intensity caudate and/or putamen lesions. The EEG shows characteristic periodic sharp wave complexes. CSF usually contains the 14-3-3 protein, and brain histologic studies reveal spongiform degeneration. No treatment is currently available.

Geschwind MD. Prion diseases. *Continuum (Minneap Minn)*. 2015;21(6):1612–1638.

Radiation Therapy

Several types of radiation therapy (RT) are currently available, and techniques continue to evolve and emerge with scientific advances. Traditional whole-brain RT, which is used to treat cerebral malignancies, is delivered in fractions over approximately 4–6 weeks. In 3-dimensional conformal RT, a computer helps concentrate radiation in a precise area; this concentration is accomplished through the use of complex asymmetric 3-dimensional shapes. Radiation surgery (radiosurgery) refers to linear accelerator or gamma knife techniques, which are distinct from traditional fractionated RT. Radiosurgery is typically given in a single sitting, using computer-based techniques to focus radiation at the desired regions. These techniques may treat malignancies, occasional inflammatory lesions, and vascular malformations. Tumors in very close proximity to the anterior visual pathway structures may not be suitable targets for single-fraction radiosurgery.

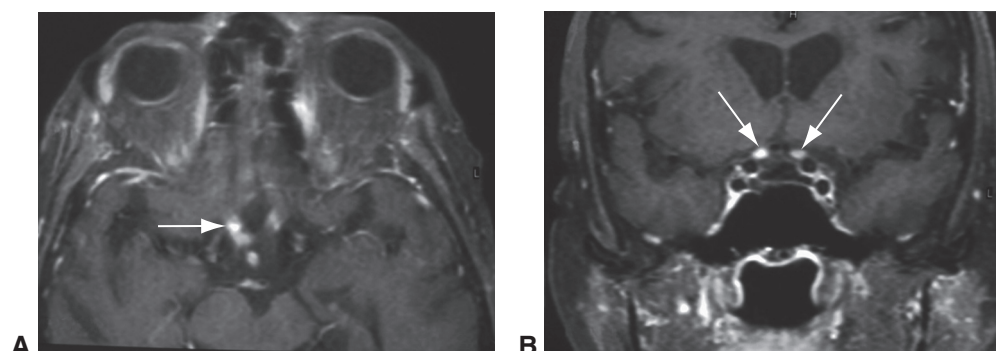


Figure 14-25 Radiation optic neuropathy (RON). **A**, Axial and **B**, coronal, T1-weighted, fat-suppressed MRI scans performed after gadolinium injection of a patient with RON. Radiation was performed for a pituitary adenoma, and months after the radiation, the patient experienced vision loss that was greater in the right eye than the left. MRI demonstrates enhancing optic nerves (arrows) in the prechiasmal region. (Courtesy of Eric Eggenberger, DO.)

Complications resulting from RT directed at the CNS may take several forms and can occur years after therapy. Immediate complications include transient swelling of the involved tissue. Later complications of neuro-ophthalmic interest include radiation necrosis, cranial neuropathies, and ocular neuromyotonia (see Chapter 7). Radiation necrosis involves death of nervous system tissue with attendant edema. This complication may simulate the imaging appearance of recurrent neoplasm on traditional MRI or CT imaging. Occasionally, functional imaging techniques such as PET or magnetic resonance spectroscopy (MRS) are required to separate these entities radiographically; neoplasms generally display a hypermetabolic profile, whereas radiation necrosis is hypometabolic in nature.

Of greater concern to the neuro-ophthalmologist is radiation optic neuropathy (RON). This rare complication typically occurs months after radiation administration and produces subacute optic neuropathy. RON is in part dose-related; it is more likely to occur with higher doses (often >5000 cGy). MRI studies of RON usually demonstrate enhancement of the optic nerve(s) on the postcontrast, T1-weighted sequences (Fig 14-25). Hyperbaric oxygen, corticosteroids, pentoxifylline, and intravenous or intravitreal bevacizumab have all been used for the treatment of RON. Thus far there is only anecdotal evidence regarding the effectiveness of such treatments.

Stroke-like migraine attacks after radiation therapy (SMART) is a syndrome related to delayed complications resulting from brain irradiation for CNS malignancies, typically occurring many years after radiation therapy. Patients present with recurrent attacks of complex neurologic signs and symptoms, including headache, visual disturbances, and seizures. Debilitating stroke-like deficits such as homonymous hemianopia, hemiplegia, and/or aphasia typically resolve over an average of 2 months; however, in some cases, the neurologic recovery is incomplete. MRI findings include unilateral increased T2 signal within the temporal, parietal, or occipital cortices with pronounced gyral cortical gray matter enhancement. As symptoms resolve, the MRI findings disappear.

Basic Texts

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Study Questions

Please note that these questions are *not* part of your CME reporting process. They are provided here for self-assessment and identification of personal professional practice gaps. The required CME posttest is available online (see “Requesting Continuing Medical Education Credit”). Following the questions are a blank answer sheet and answers with discussions. Although a concerted effort has been made to avoid ambiguity and redundancy in these questions, the authors recognize that differences of opinion may occur regarding the “best” answer. The discussions are provided to demonstrate the rationale used to derive the answer. They may also be helpful in confirming that your approach to the problem was correct or, if necessary, in fixing the principle in your memory. The Section 5 faculty thanks the Self-Assessment Committee for reviewing these self-assessment questions.

1. Which of the following nerves is located outside of the cavernous sinus?
 - a. optic
 - b. oculomotor
 - c. abducens
 - d. oculosympathetic
2. What is the correct routing of the fibers that control the pupillary response to light?
 - a. retina to Edinger-Westphal nuclei to pretectal nuclei to ciliary ganglion to pupilloconstrictor fibers
 - b. retina to Edinger-Westphal nuclei to pretectal nuclei to sympathetic ganglion to pupilloconstrictor fibers
 - c. retina to pretectal nuclei to Edinger-Westphal nuclei to sympathetic ganglion to pupilloconstrictor fibers
 - d. retina to pretectal nuclei to Edinger-Westphal nuclei to ciliary ganglion to pupilloconstrictor fibers
3. Nephrogenic systemic fibrosis (NSF) caused by the use of a gadolinium-based contrast agent is most likely to occur with what systemic condition?
 - a. heart disease
 - b. lung disease
 - c. kidney disease
 - d. liver disease
4. What is the most important reason that magnetic resonance imaging (MRI) should not be performed on a patient with a metallic foreign body in the eye?
 - a. increased exposure to ionizing radiation
 - b. difficulty obtaining sagittal images
 - c. potential for dislodging the metallic foreign body
 - d. overestimation of the size of the metallic foreign body

5. The blood oxygenation level–dependent (BOLD) technique is used with which of the following imaging modalities?
 - a. functional MRI (fMRI)
 - b. magnetic resonance spectroscopy (MRS)
 - c. positron emission tomography (PET)
 - d. single-photon emission computed tomography (SPECT)
6. Visual evoked potential (VEP) testing is most helpful in the diagnosis of which condition?
 - a. glaucoma
 - b. compressive optic neuropathy
 - c. demyelinating optic neuropathy
 - d. cone dystrophy
7. A patient who presents with optic nerve head (ONH) swelling and delayed choroidal filling on fluorescein angiography will most likely have what condition?
 - a. giant cell arteritis
 - b. bartonella neuroretinitis
 - c. optic nerve sheath meningioma
 - d. demyelinating optic neuritis
8. What examination finding is more suggestive of an optic neuropathy than a retinopathy?
 - a. abnormal color vision
 - b. large relative afferent pupillary defect
 - c. central scotoma
 - d. mild optic nerve head pallor
9. What is the best predictor for the future risk of multiple sclerosis (MS) in a patient after a first episode of optic neuritis?
 - a. enhancement of the optic nerve on orbital MRI
 - b. periventricular white-matter lesions on brain MRI
 - c. oligoclonal bands in the cerebrospinal fluid
 - d. worsening of vision with exercise (Uhthoff phenomenon)
10. ONH drusen are most frequently associated with what examination finding?
 - a. peripheral visual field constriction
 - b. ONH edema
 - c. cystoid macular edema
 - d. peripapillary choroidal neovascular membrane

11. What symptom should suggest arteritic anterior ischemic optic neuropathy in a patient with an acute optic neuropathy?
 - a. sudden vision loss
 - b. pain that accompanies eye movements
 - c. prior transient monocular visual loss
 - d. severe color vision deficit
12. A young man presents with recurrent episodes of transient monocular visual loss in the right eye following a car accident. He also reports experiencing ipsilateral headache. What clinical finding is highly suggestive of a right internal carotid artery dissection?
 - a. left hemiparesis
 - b. right retinal emboli
 - c. diplopia
 - d. right Horner syndrome
13. Damage to what anatomical pathway causes Balint syndrome?
 - a. medial longitudinal fasciculus
 - b. ventral occipitotemporal
 - c. dorsal occipitoparietal
 - d. optic tract
14. What is the term for the illusion of an object that moves in an elliptical path rather than a straight line following a bout of demyelinating optic neuritis?
 - a. Riddoch phenomenon
 - b. Pulfrich phenomenon
 - c. palinopsia
 - d. optic ataxia
15. A lesion to what area of the brain causes the combination of symptoms of formed hallucinations, insomnia, and excessive daytime somnolence?
 - a. nondominant parieto-occipital cortex
 - b. midbrain
 - c. temporal lobe
 - d. occipital lobe
16. Which of the following clinical signs is expected in patients with bilateral fourth cranial nerve (CN IV) palsies?
 - a. intorsion of the hypertropic eye
 - b. chin up position
 - c. V-pattern esotropia
 - d. hypertropia that worsens on upgaze

17. During ocular motility testing, a patient develops episodic diplopia, seen as transient right exotropia in primary gaze after maintaining both eyes in extreme right gaze for several seconds. What is the most likely medical history that led to this ocular motility abnormality?
 - a. poorly controlled diabetes mellitus treated with oral hypoglycemic
 - b. progressive MS treated with glatiramer acetate
 - c. metastatic breast cancer treated with tamoxifen
 - d. tuberculum sellae meningioma treated with radiation therapy
18. In a patient with CN IV palsy, what finding would place the lesion at the nuclear/predecussation fascicular level?
 - a. ipsilateral Horner syndrome
 - b. ipsilateral relative afferent pupillary defect
 - c. homonymous hemianopia
 - d. ipsilateral facial weakness
19. What examination finding is consistent with aberrant regeneration of CN III?
 - a. eyelid retraction with supraduction
 - b. eyelid retraction with adduction
 - c. pupillary mydriasis with adduction
 - d. pupillary miosis with abduction
20. What brainstem structure is responsible for generating horizontal saccades?
 - a. medial longitudinal fasciculus
 - b. paramedian pontine reticular formation
 - c. interstitial nucleus of Cajal
 - d. rostral interstitial nucleus of the medial longitudinal fasciculus
21. Congenital ocular motor apraxia is characterized by dysfunction in initiating what type of eye movement?
 - a. vertical smooth pursuit
 - b. horizontal smooth pursuit
 - c. vertical saccades
 - d. horizontal saccades
22. Which of the following conditions is the most common cause of divergence insufficiency in an otherwise healthy adult patient?
 - a. CN VI nucleus ischemia
 - b. connective tissue involution between the superior and lateral rectus muscles
 - c. medial longitudinal fasciculus demyelination
 - d. medial rectus muscle enlargement

23. A patient who presents with jerk nystagmus worse in down and lateral gaze to either side is most likely to have a lesion affecting what structure?
- medulla
 - dorsal midbrain
 - diencephalon
 - flocculus of the cerebellum
24. What is the potential cause for an infant presenting with a conjugate horizontal nystagmus with a null point and reversal of the normal pattern of optokinetic nystagmus (OKN)?
- intracranial tumor
 - bilateral pregeniculate visual loss
 - poor binocular fusion
 - optic nerve glioma
25. Dorsal midbrain syndrome classically includes what ocular motility abnormality?
- square-wave jerks
 - opsoclonus-myoclonus syndrome
 - convergence-retraction nystagmus
 - ocular flutter
26. A lesion in which area results in a Horner pupil that is associated with ipsilateral impairment of pain and temperature sensation over the face and contralateral impairment of pain and temperature sensation over the trunk and limbs?
- cavernous sinus lesion
 - internal carotid artery dissection
 - lateral medullary injury
 - congenital brachial plexus injury
27. Anisocoria that is greater in the light than in the dark that does not respond to pilocarpine 1% is most likely due to what condition?
- physiologic anisocoria
 - pharmacologic pupillary dilation
 - Adie pupil
 - CN III palsy
28. What drug can be used to confirm the presence of a Horner pupil?
- Hydroxyamphetamine
 - Brimonidine
 - Apraclonidine
 - Pilocarpine

29. Congenital Horner syndrome is commonly due to what condition?
 - a. brachial plexus injury
 - b. internal carotid artery aneurysm
 - c. cavernous sinus tumor
 - d. spinal cord tumor
30. A patient presents with facial weakness, diplopia, ataxia, and areflexia. What is the most likely cause?
 - a. Miller Fisher syndrome
 - b. Ramsay Hunt syndrome
 - c. Melkersson-Rosenthal syndrome
 - d. a cerebellopontine angle tumor
31. A patient presents with continuous unilateral undulating contraction of the orbicularis oculi and most of the facial muscles. What is the most common cause of these symptoms?
 - a. vascular compression of CN VII
 - b. pontine glioma
 - c. excessive caffeine intake
 - d. aberrant regeneration resulting from prior Bell palsy
32. What is the preferred order of surgical procedures for a patient with severe thyroid eye disease that requires multiple surgeries?
 - a. orbital decompression, eyelid surgery, strabismus surgery
 - b. strabismus surgery, orbital decompression, eyelid surgery
 - c. orbital decompression, strabismus surgery, eyelid surgery
 - d. eyelid surgery, strabismus surgery, orbital decompression
33. A patient with what disorder is most likely to present with bilateral eyelid involvement?
 - a. dorsal midbrain syndrome
 - b. idiopathic levator fibrosis
 - c. Marcus Gunn jaw-winking syndrome
 - d. spastic paretic facial contracture
34. What clinical manifestation would raise concern for a structural intracranial lesion in a patient with presumed typical aura without headache (previously termed acephalgic migraine)?
 - a. visual aura
 - b. persistent hemianopic visual field defect
 - c. positive visual phenomena on one side of vision
 - d. history of migraines in young adulthood

35. What is a common finding in primary trigeminal neuralgia?
- involvement of CN V₁
 - bilateral symptoms
 - facial numbness
 - stabbing pain for a short duration
36. A 45-year-old man presents with several episodes per day of severe left-sided orbital and temporal pain that lasts 5–10 minutes, occasionally associated with left ptosis and miosis. What is the most likely diagnosis?
- cluster headache
 - paroxysmal hemicrania
 - hemicrania continua
 - idiopathic stabbing headache
37. What test finding is most helpful in establishing the presence of some vision in a patient with suspected nonorganic vision loss who claims to see nothing in both eyes?
- no eye movement with the mirror test
 - abnormal proprioceptive tests, including the finger-touching test
 - eye movement with rotation of an OKN drum
 - absence of a relative afferent pupillary defect
38. A 61-year-old taxi driver reports contracted vision in both eyes, which has caused difficulty while driving for almost 2 months. Visual acuity is normal, and kinetic perimetry shows a diffuse generalized constricted visual field with a 10° central island in both eyes. Tangent screen tests at 1 and 2 meters do not show any change in the size of the defect. What is the most likely cause of the constricted fields?
- retinitis pigmentosa
 - glaucoma
 - bilateral occipital lobe stroke
 - nonorganic vision loss
39. What best describes an eye movement characterized by irregular, brief bursts of rapid frequency and low amplitude, with no slow phase?
- end gaze nystagmus
 - voluntary flutter
 - spasm of the near reflex
 - see-saw nystagmus
40. What maneuver can be used to diagnose a patient with suspected nonphysiologic ptosis?
- ask the patient to look up
 - ask the patient to look down
 - ask the patient to look down for a few seconds and then refixate straight ahead
 - ask the patient to make horizontal saccades and measure the palpebral fissures

41. What disease-modifying therapy has been most often associated with a progressive alteration of mental status resulting from a homonymous hemianopia in a patient with MS?
 - a. fingolimod
 - b. glatiramer acetate
 - c. natalizumab
 - d. interferon β -1a
42. What neuroimaging finding is characteristic of tuberous sclerosis?
 - a. intracranial calcified hamartoma
 - b. acoustic neuroma
 - c. cerebellar hemangioblastoma
 - d. leptomeningeal vascular malformation
43. A 28-year-old previously healthy woman presents with acute onset of vision loss in the right eye associated with pain on ocular movement. MRI scans of the brain and orbits show enhancement of the right optic nerve and 5 periventricular white-matter lesions. What pharmaceutical agent has been shown to reduce her risk of developing clinically definite MS in the future?
 - a. fingolimod
 - b. intravenous immunoglobulin
 - c. natalizumab
 - d. glatiramer acetate
44. A 48-year-old woman suddenly develops painful vision loss in her right eye. Two weeks later, she develops similar symptoms in her left eye. Her examination shows visual acuity when counting fingers with the right eye and hand motion with the left eye, no relative afferent pupillary defect but sluggish pupils, normal dilated examination in the right eye and mild ONH edema in the left eye. MRI shows bilateral enhancement of the optic nerves. After treatment with IV methylprednisolone, she experiences only minimal vision recovery. What underlying condition is the most likely cause of her bilateral vision loss?
 - a. MS
 - b. neuromyelitis optica
 - c. giant cell arteritis
 - d. adverse effect of fingolimod treatment
45. What is the most appropriate study for a patient who presents with headache, mild ipsilateral ptosis, and amaurosis fugax 4 days following a motor vehicle accident?
 - a. computed tomography (CT) scan of the brain and orbits
 - b. bilateral carotid Doppler study
 - c. ultrasound of the orbit
 - d. computed tomography angiography (CTA) of the neck

Answer Sheet for Section 5

Study Questions

Question	Answer	Question	Answer
1	a b c d	24	a b c d
2	a b c d	25	a b c d
3	a b c d	26	a b c d
4	a b c d	27	a b c d
5	a b c d	28	a b c d
6	a b c d	29	a b c d
7	a b c d	30	a b c d
8	a b c d	31	a b c d
9	a b c d	32	a b c d
10	a b c d	33	a b c d
11	a b c d	34	a b c d
12	a b c d	35	a b c d
13	a b c d	36	a b c d
14	a b c d	37	a b c d
15	a b c d	38	a b c d
16	a b c d	39	a b c d
17	a b c d	40	a b c d
18	a b c d	41	a b c d
19	a b c d	42	a b c d
20	a b c d	43	a b c d
21	a b c d	44	a b c d
22	a b c d	45	a b c d
23	a b c d		

Answers

1. **a.** The oculosympathetic nerves and cranial nerves (CNs) III, IV, V, and VI are all contained within the cavernous sinus; the optic nerve is not. CNs III, IV, and V are located within the lateral wall of the cavernous sinus. CN VI is located inside the cavernous sinus.
2. **d.** The pupillary response to light is mediated by parasympathetic neurons and involves midbrain pretectal nuclei that send fibers to the Edinger-Westphal subnuclei of the CN III nucleus. The parasympathetic fibers synapse in the ciliary ganglion before projecting in the short ciliary nerve to the iris sphincter.
3. **c.** Nephrogenic systemic fibrosis (NSF) is often seen in patients with kidney disease. The risk of NSF increases with lower glomerular filtration rate because the kidneys are primarily responsible for clearing gadolinium contrast. Chronic liver disease is not a significant risk factor for NSF. Heart and lung disease are not associated with NSF.
4. **c.** The magnetic field may dislodge a metallic foreign body. In patients with intraocular metallic foreign bodies, this may result in severe damage to the eye. Exposure to ionizing radiation and lack of sagittal imaging are problems associated with computed tomography (CT) scans. Overestimation of vascular stenosis can occur with magnetic resonance angiography (MRA) scans.
5. **a.** Functional magnetic resonance imaging (fMRI) depends on changes in regional blood flow in the brain in response to metabolic demand. The basis for most fMRI is measurement of differences in blood oxygenation level–dependent (BOLD) responses during performance of specific tasks such as speech or finger movement. This method uses the change in magnetic susceptibility of hemoglobin (Hb) as it changes from oxyHb (diamagnetic) to deoxyHb (paramagnetic) and is followed by an increase in cerebral blood flow. Magnetic resonance spectroscopy (MRS) is used to assess the metabolism and integrity of neural tissue in vivo. Positron emission tomography (PET) shows metabolic perfusion and is performed with systemically administered radioisotopes with a short half-life followed by imaging of the positrons produced during their decay. Finally, single-photon emission computed tomography (SPECT) uses an iodinated radiotracer or technetium-99m to assess cerebral perfusion and metabolism.
6. **c.** Visual evoked potential (VEP) testing measures electrical signals over the occipital cortex produced in response to a visual stimulus. It shows an increased latency in demyelination. Other optic neuropathies generally have a normal latency but may show a decrease in the VEP's amplitude.
7. **a.** Angiography may demonstrate delayed or absent choroidal filling in a patient with giant cell arteritis. This may be either with or without optic nerve head (ONH) edema. Other causes of optic nerve swelling may show ONH leakage on angiography but will not show delayed choroidal filling.
8. **b.** A large relative afferent pupillary defect is highly suggestive of unilateral or asymmetric optic neuropathy. A mild relative afferent pupillary defect can be seen with significant asymmetric retinal damage involving the macula. Color vision may be altered in patients with maculopathies or optic neuropathies. A central scotoma may be seen in both maculopathies and optic neuropathies. Mild optic nerve head pallor is common in numerous chronic retinopathies such as cone dystrophies.

9. **b.** An abnormal brain magnetic resonance imaging (MRI) scan showing at least one white-matter lesion consistent with demyelinating disease is the best predictor of multiple sclerosis (MS) in patients after a first episode of optic neuritis. The risk for developing MS is estimated at 72% after 15 years in patients with presence of abnormalities on MRI compared with approximately 25% in patients with normal brain MRI at presentation.
10. **a.** Nerve fiber bundle defects leading to constriction of visual fields are often observed on perimetry of patients with ONH drusen but are rarely noticed by patients. ONH edema typically only occurs with another optic nerve disorder. Drusen are not associated with cystoid macular edema. Peripapillary choroidal neovascular membranes are very rare and can produce severe visual loss when they bleed.
11. **c.** Arteritic anterior ischemic optic neuropathy causes isolated, sudden, permanent vision loss, often preceded by or associated with episodes of transient visual loss or episodes of transient diplopia.
12. **d.** An acute painful Horner syndrome is highly suggestive of an ipsilateral internal carotid artery dissection, especially in a patient with recurrent episodes of transient monocular visual loss. Hemiparesis contralateral to the eye involved or retinal emboli in the affected eye both suggest a possible internal carotid artery stenosis, but these findings are not specifically suggestive of dissection. Diplopia should be expected with vascular events in the posterior circulation.
13. **c.** The dorsal occipitoparietal pathway is the “where” pathway; it is responsible for visuo-spatial analysis, localization of objects, and visually directed movements toward objects. Balint syndrome results from bilateral occipitoparietal lesions and consists of the triad of simultanagnosia, optic ataxia, and ocular motor apraxia. Lesions of the medial longitudinal fasciculus produce internuclear ophthalmoplegia. The ventral occipitotemporal pathway is the “what” pathway, which is responsible for color, shape, and pattern recognition. Lesions of the bilateral ventral occipitotemporal pathway cause object agnosia. Lesions of the optic tract cause complete or incomplete homonymous hemianopia.
14. **b.** Due to the relative conduction delay within an optic nerve that has been affected by demyelinating optic neuritis compared with the contralateral unaffected optic nerve, an object moving in a single plane may be perceived as tracing an elliptical rather than straight path. This illusion is referred to as the Pulfrich phenomenon. Riddoch phenomenon refers to the ability to see moving but not static objects in a blind hemifield (statico-kinetic dissociation). Palinopsia is the perseveration of a visual image after removal of the original stimulus. Optic ataxia is the inability to perform visually guided movements.
15. **b.** In rare cases, lesions involving the mesencephalon (midbrain) cause formed, often constant hallucinations frequently associated with an inverted sleep-wake cycle (peduncular hallucinosis). There may be accompanying neurologic symptoms depending on the extent of the midbrain lesion. Disorders of the nondominant parieto-occipital area cause palinopsia, the illusion of persistent afterimages that may be associated with visual hallucinations. Temporal lobe lesions most often produce olfactory and gustatory hallucinations, and visual phenomena from this area are usually complex, formed hallucinations in the ipsilateral or contralateral visual field. Occipital lobe lesions commonly cause unformed hallucinations, which are sometimes described as geometric colors or patterns.
16. **c.** The superior oblique muscle intorts, depresses, and abducts the eye. A patient with a bilateral CN IV palsy presents with crossed hypertropia (right hypertropia on left gaze

and left hypertropia on right gaze), extorsion of at least 10°, a large V-pattern esotropia (esotropia greatest on downgaze), and chin down positioning (as hypertropia decreases in upgaze). Intorsion of the hypertropic eye accompanies a skew deviation in the ocular tilt reaction.

17. **d.** Ocular neuromyotonia, in which episodic diplopia lasting 30–60 seconds develops after sustained activation of a cranial ocular motor nerve, is usually associated with a history of radiation therapy for a skull-based neoplasm.
18. **b.** A lesion of the brachium of the superior colliculus will produce a relative afferent pupillary defect in the absence of color vision loss or a visual field defect. The relative afferent pupillary defect will be ipsilateral to the CN IV palsy due to the decussation of nasal pupillary fibers at the chiasm and the decussation of CN IV after it exits the brainstem. A contralateral Horner syndrome may occur due to the proximity of the descending sympathetic fibers. A homonymous hemianopia would not occur with a pure brainstem injury. Ipsilateral facial weakness would not localize to the midbrain.
19. **b.** Aberrant regeneration of CN III occurs after damage results in regrowth and misrouting of fibers with innervation of muscles not normally activated together. This causes abnormal synkinetic phenomenon such as eyelid retraction with adduction or pupillary miosis with supraduction, adduction, or infraduction. Eyelid retraction with supraduction is a normal response to CN III activation. Aberrant regeneration of CN III is common after traumatic injury but may also occur with compressive lesions such as aneurysms or tumors. Microvascular ischemic CN III does not cause aberrant regeneration.
20. **b.** The excitatory burst neurons for generating horizontal saccades are located in the paramedian pontine reticular formation. The medial longitudinal fasciculus contains neurons that project from the CN VI nucleus to the contralateral CN III nucleus and mediates horizontal yoke muscle movement. The rostral interstitial nucleus of the medial longitudinal fasciculus and the interstitial nucleus of Cajal are located in the midbrain and are involved in the generation of torsional and vertical saccades.
21. **d.** Congenital ocular motor apraxia (as described by Cogan) is idiopathic and is characterized by increased latency and intermittent failure of horizontal saccadic initiation. Vertical eye movements are normal.
22. **b.** Divergence insufficiency (DI) is an acquired ocular misalignment defined by an esodeviation that is greater at distance than near fixation, without lateral incomitance, and without abduction deficits. This disorder is usually benign and not related to neurologic dysfunction. In older patients, DI often results from involution of the connective tissue band between the superior and lateral rectus muscles, causing inferior displacement of the lateral rectus muscles (ie, sagging eye syndrome). The malpositioned lateral rectus muscles have reduced abduction force, resulting in DI pattern esotropia. Rarely, DI may be caused by neurological disorders such as increased intracranial pressure, midbrain tumors, Miller Fisher syndrome, head trauma, intracranial hypotension, Arnold-Chiari malformation, and cerebellar degeneration (often with other signs of these disorders). A lesion in the CN VI nucleus results in a gaze palsy. A lesion in the medial longitudinal fasciculus results in an internuclear ophthalmoplegia characterized by impaired adduction and an abducting nystagmus during horizontal gaze opposite the side of the lesion. Enlarged medial rectus muscles that impair abduction are characteristic of thyroid-related orbitopathy.

23. **d.** Downbeat nystagmus results from lesions that compromise the vestibulocerebellum (ie, the nodulus, uvula, flocculus, and paraflocculus of the cerebellum). Examples of other localizing forms of central vestibular nystagmus are upbeat nystagmus (medulla), Parinaud syndrome (dorsal midbrain), and see-saw nystagmus (parasellar region/diencephalon).
24. **b.** True infantile nystagmus syndrome (INS), or congenital nystagmus (CN), is not associated with afferent pathway disease and does not produce oscillopsia. In contrast, sensory nystagmus, which has a similar presentation, arises when central visual acuity is too poor to develop a stable fixational mechanism. It is associated with conditions that cause bilateral, pregeniculate vision loss in children younger than 2 years. Therefore, workup of a patient with early-onset nystagmus should include a search for clinical manifestations of pregeniculate vision loss. In the absence of obvious ocular causes such as cataract, the patient should be evaluated for the following conditions, which may be subtle and difficult to detect in uncooperative children: optic neuropathy, foveal hypoplasia, and retinal dystrophy. Intracranial brain tumors do not cause INS. Poor fusion in a child causes fusion maldevelopment nystagmus. Chiasmal/suprachiasmal tumors such as optic pathway gliomas may result in a nystagmus identical to spasmus nutans.
25. **c.** The presence of convergence-retraction nystagmus localizes the disease process to the dorsal midbrain; it is part of dorsal midbrain syndrome. Convergence-retraction nystagmus results from co-contraction of the extraocular muscles on attempted upgaze; the co-contraction of all extraocular muscles causes the globe to retract into the orbit. Dorsal midbrain syndrome also includes lid retraction, upgaze deficit, and pupillary light–near dissociation. Square-wave jerks, opsoclonus-myoclonus syndrome, and ocular flutter are not components of dorsal midbrain syndrome.
26. **c.** Lateral medullary syndrome (Wallenberg syndrome) produces an ipsilateral Horner syndrome, ipsilateral impairment of pain and temperature sensation over the face (involvement of the descending tract of CN V), contralateral impairment of pain and temperature sensation over the trunk and limbs (involvement of the lateral spinal thalamic tract), ipsilateral cerebellar ataxia (damage to spinocerebellar tracts), and the ocular tilt reaction. In addition, patients with lateral medullary syndrome may have dysarthria, dysphagia, vertigo, persistent hiccups, lateropulsion, and ocular lateropulsion. A cavernous sinus lesion, an internal carotid artery dissection, or a congenital brachial plexus injury might cause Horner syndrome, but they would not also cause the crossed impaired sensation of pain and temperature of the face and rest of the body.
27. **b.** A patient with pharmacologic pupillary dilation will present with anisocoria that is greater in the light that does not respond to full strength pilocarpine (1% or more). Mydriasis due to Adie pupil or CN III palsy is overcome with installation of dilate or full-strength pilocarpine, respectively.
28. **c.** Instilling apraclonidine in both eyes of a patient with Horner syndrome causes reversal of anisocoria due to the development of denervation supersensitivity of the α_1 -receptor, which makes the pupil dilator responsive to the weak α_1 effect of apraclonidine. Hydroxyamphetamine is used to localize the Horner syndrome to either pre- or postganglionic. Brimonidine, which is a relatively pure α_2 -agonist, has no significant α_1 -adrenergic effect and therefore does not produce pupil dilation.
29. **a.** Congenital Horner syndrome is most commonly caused by birth trauma to the brachial plexus. If there is no history of trauma, then the patient should have a workup for congenital tumors, such as neuroblastoma.

30. **a.** Areflexia, ataxia, and ophthalmoplegia characterize Miller Fisher syndrome, a variant of Guillain-Barré syndrome, and facial diplegia often accompanies this classic triad. Herpes zoster involving CN VII is called Ramsay Hunt syndrome. It is diagnosed by the identification of vesicles along the posterior aspect of the external auditory canal. Melkersson-Rosenthal syndrome presents as recurrent unilateral or bilateral facial paralysis and is accompanied by chronic facial swelling. A cerebellopontine angle tumor may present with facial palsy, diplopia, hearing loss, and nystagmus.
31. **b.** Facial myokymia is usually the result of a pontine glioma or demyelination (ie, MS). It is characterized by continuous unilateral contraction of facial muscle bundles and typically signifies intramedullary disease of the pons involving the CN VII nucleus or fascicle. Compression of the CN VII root exit zone by an aberrant vessel is the most common cause of hemifacial spasm, which is characterized by a unilateral episodic spasm involving the facial musculature. Excessive caffeine intake may cause isolated eyelid myokymia. Aberrant regeneration after facial palsy is typically not continuous.
32. **c.** Orbital decompression will often alter or augment preexisting strabismus, so it should always precede strabismus surgery. Similarly, the strabismus surgery often alters the position of the eyelids, particularly the inferior eyelids. Eyelid surgery should be the last step.
33. **a.** Bilateral eyelid retraction (Collier sign) can be seen in patients with dorsal midbrain syndrome. Idiopathic levator fibrosis, Marcus Gunn jaw-winking syndrome, and spastic parietic facial contracture are associated with unilateral eyelid abnormalities.
34. **b.** Visual auras associated with migraines are usually hemianopic and often include positive visual phenomena. Visual aura typically lasts less than 60 minutes. The presence of a persistent hemianopic visual field defect may indicate that the symptoms are caused by an irritative mass lesion.
35. **d.** Primary trigeminal neuralgia is typically caused by vascular compression of CN V. It is almost always unilateral and usually involves the maxillary or mandibular distribution of CN V. Sensory function in the face should be normal on testing. Involvement of CN V₁, bilateral symptoms, and facial numbness are more commonly seen in secondary trigeminal neuralgia; these symptoms raise the concern for an infiltrative or another pathological lesion.
36. **b.** Paroxysmal hemicrania is a form of trigeminal autonomic cephalgia associated with short bouts of pain highly responsive to indomethacin. Although cluster headache is also unilateral and frequently associated with autonomic features, the bouts of excruciating pain are of longer duration (15–180 minutes). Hemicrania continua is characterized by a continuous unilateral headache. Idiopathic stabbing headache manifests as episodic, very brief, sharp, jabbing pains, unassociated with autonomic features.
37. **c.** The optokinetic nystagmus (OKN) drum test is perhaps the easiest test to perform and can help document the presence of some vision in patients who claim total bilateral blindness. In a patient with nonorganic blindness, some vision can also be confirmed via documentation of eye movements during the mirror test and abnormal responses to proprioceptive tests such as the finger-touching test. Because a relative afferent pupil defect can be absent in bilateral disease, it does not prove nonorganic vision loss.
38. **d.** Tunnel vision that does not expand on a tangent field at 1 and 2 meters is characteristic of nonorganic vision field loss. Furthermore, no other eye findings in this case support an organic pathology. Organic visual field loss should demonstrate a funnel of vision rather

than tunnel vision (ie, the field expands as testing is executed at distances farther away from the patient).

39. **b.** Voluntary flutter, sometimes misdiagnosed as nystagmus, is characterized by irregular, brief bursts of rapid frequency and low-amplitude eye movements with no slow phase. Voluntary flutter is usually seen in patients with nonorganic motility disturbances. End gaze nystagmus has a fast and slow phase; spasm of the near reflex is characterized by episodes of intermittent convergence, increased accommodation, and miosis. See-saw nystagmus is a form of disconjugate nystagmus in which 1 eye elevates and intorts and the other eye depresses and extorts, like a see-saw.
40. **a.** Patients who feign ptosis generally cannot simultaneously elevate the eye and maintain a drooping eyelid. Thus, with upward gaze, the ptosis will “resolve.” Looking down is not as effective for this purpose. Asking the patient to look down for a few seconds and then refixate straight ahead is a way to evaluate the patient for Cogan lid-twitch sign, which may be present in patients with myasthenia gravis. Asking a patient to make horizontal saccades and measure the palpebral fissures is used for the evaluation of aberrant regeneration or Duane retraction syndromes.
41. **c.** Altered mental status in the presence of a hemianopic visual field defect raises concern for progressive multifocal leukoencephalopathy, a condition associated with natalizumab in patients who are JC-virus positive. The other therapies have either not been associated or have only been associated with encephalopathy in rare cases. Fingolimod can cause macular edema.
42. **a.** Tuberous sclerosis is associated with intracranial calcified astrocytic hamartomas. Acoustic neuroma is the classic neuroimaging finding for neurofibromatosis type 2. Cerebellar hemangioblastoma is associated with von Hippel–Lindau disease. Leptomeningeal vascular malformation is a feature of Sturge–Weber syndrome (encephalofacial angiomatosis).
43. **d.** Because this is the patient’s first demyelinating episode, she has a clinically isolated syndrome (CIS). Treatment with interferon β -1a, interferon β -1b, and glatiramer acetate has been shown to delay conversion to clinically definite MS in patients with CIS who have 2 or more white-matter lesions. Fingolimod, intravenous immunoglobulin, and natalizumab are not recommended for treatment of a patient with CIS.
44. **b.** This vision loss is most consistent with bilateral optic neuritis. The bilateral nature of the vision loss, along with the severity of visual impairment and minimal recovery after treatment, raise a concern for neuromyelitis optica. It is uncommon for MS to present with bilateral optic neuritis with minimal recovery. Giant cell arteritis can cause bilateral severe vision loss associated with headache, but it does not affect young patients. Fingolimod has been associated with macular edema, which would cause blurred vision but not this degree of vision loss.
45. **d.** The patient’s history and clinical findings are very concerning for an internal carotid artery dissection. Both MRI/MRA and computed tomography angiography (CTA) are used to detect a carotid dissection. CTA is often used in the acute setting because it is faster. CT of the brain and orbits would not be sensitive enough to detect a carotid dissection. Ultrasound is not adequate for detecting arterial dissection and can elicit a false-negative result in nearly one-third of cases.

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